RICE

NASA Specialized Center of Research and Training (NSCORT) in Gravitational Biology

Rice University
Institute of Biosciences and Bioengineering
Houston, Texas

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Year One Progress Report

Covering the Period:
March 1, 1996 - December 31, 1996

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The NASA Specialized Center of Research and Training (NSCORT) in Gravitational Biology at Rice University's Institute of Biosciences and Bioengineering was officially initiated March 1, 1996. We are pleased to submit this report on the progress made during the first year of our NSCORT and our plans for the coming year.

MISSION STATEMENT

The mission of our NSCORT is to investigate the effects of gravity and other environmental factors on biological function at the cellular and molecular level. The research efforts, training opportunities, and scientific exchange will promote the expansion of a scientific peer group well-educated in space-related biological issues. This will stimulate the interest of the larger scientific community and insure the continuing development of rigorous flight investigations in Gravitational Biology.

RESEARCH OVERVIEW

The Rice NSCORT research program is focused on examining the effects of microgravity and associated stresses on development and cell culture in prokaryotes and eukaryotes. While most of the research involves mammalian cells, exciting research is also underway on plant cells, yeasts, microbial cells and *Drosophila melanogastor*. Many of the projects include utilization of the rotating bioreactor systems developed at Johnson Space Center as a tool for simulation of some aspects of the microgravity environment.

Several of the project principal investigators have established research programs centered on understanding the molecular basis of the response of various cell types to mechanical stimuli. These faculty include Professor Braam (employing a plant model), Professor Gustin (using yeast) and Professor McIntire (mammalian cells). The NSCORT research program is centered on understanding at the molecular and cellular level, the effect of microgravity and associated stresses on development and cell function. Drosophila are chosen as the model system for two of the developmental biology projects because of the wealth of molecular level knowledge and reagents that are available to allow testing of very specific mechanistic hypotheses (Projects I and II). In addition, this model system is relatively easy to translate to actual flight experiments once ground-based research identifies the proper questions to ask and establishes the requisite data base for comparison.

Projects III, IV and V examine basic cellular mechanisms involved in sensing the mechanical force environment, in transduction of these signals, and in gene regulation, using arabidopsis, yeast and mammalian cell models. These projects interact closely with each other because of their common scientific interest in signal transduction and the understanding produced forms a mechanistic basis for developing hypotheses concerning the effect of microgravity on cell function. The data produced will also have wide application in many other areas where mechanical forces are intimately coupled with gene regulation and cell metabolism.

The remaining four projects currently underway examine specific hypotheses focused on understanding the molecular and cellular basis of several documented cellular alterations seen in space flight. These include a dramatic reduction in lymphocyte DNA synthesis in response to mitogens (Project VI) and in migration (Project IX), increased bone resorption and demineralization (Project VII), and skeletal muscle atrophy (Project VIII).

The model systems have been carefully chosen so that specific mechanistic questions at the cellular and molecular level can be addressed and so that once the proper ground-based data have been assembled, the development of flight based proposals will not be difficult.

These projects span a sufficient range of areas to be attractive to a wide range of potential trainees - undergraduate, graduate students and postdoctoral fellows. Too narrow a focus would limit the attraction of the NSCORT and we would not be able to interest the highest quantity young scientists and engineers we are currently attracting.

MANAGEMENT OVERVIEW

The NSCORT is administered by the Institute of Biosciences and Bioengineering at Rice University and involves significant participation from two of the three Laboratories in the Institute as well as the NASA Johnson Space Center.

Administration: Day-to-day decisions regarding budgeting and programmatic matters are handled by the NSCORT Director in consultation with the Associate Director. Oversight of day-to-day administrative operations and the development and implementation of education and outreach activities are handled by the Assistant Director of the Institute. Secretarial support for the NSCORT is also provided through the Institute.

Executive Committee: An Executive Committee has been established to examine new budget requests and to evaluate research progress. The committee members are listed below. This committee is also responsible for assigning students and fellows to individual projects and for evaluation of equipment requests to be funded out of the "competitive equipment" budget category. The committee meets bimonthly in conjunction with the NSCORT bimonthly seminar series at which NSCORT faculty provide a detailed presentation of their research progress.

Executive Committee Members

Larry V. McIntire, E.D. Butcher Professor of Biomedical Engineering and Chair, Institute of Biosciences and Bioengineering, Rice University

Frederick B. Rudolph, Professor and Chair of Biochemistry and Cell Biology and Executive Director, Institute of Biosciences and Bioengineering, Rice University

Kathleen Beckingham, Professor of Biochemistry and Cell Biology, Rice University

James Kinsey, Dean, School of Natural Sciences, Rice University

Clarence Sams, Research Biochemist, Biomedical Operations and Research Branch, NASA, Johnson Space Center

Nitza Cintron, Research Biochemist, Biomedical Operations and Research Branch, NASA, Johnson Space Center

External Review Committee: We are in the process of finalizing the membership of our External Advisory Committee, which will be in place and hold its first meeting during our First Annual NSCORT Symposium to be held in Spring 1997. As discussed in our initial proposal, the committee will meet on a yearly basis to evaluate program progress and direction and give guidance to the Director and the Executive Committee. The External Review Committee will also review and evaluate requests for new research proposals in conjunction with the Executive Committee.

Budget: The budget request for Year Two of our NSCORT (March 1, 1997 - February 28, 1998) remains unchanged from that proposed in a revised management plan and budget letter to Dr. Ron White dated October 29, 1995 and approved by NASA. In this budget, funds for Year Two would be allocated as follows: $843,567 to Rice University and $156,433 to the Johnson Space Center. A more detailed budget request can be submitted if required.

RESEARCH PROGRESS REPORTS

In this first year of our NSCORT nine research projects were funded. Progress reports for each of these projects follow. The reports cover the period March 1, 1996 (the date our NSCORT was officially initiated) through December 1996.

PROJECT I

"The Role of Gravity in Early Embryonic Pattern Formation"

Kathleen Beckingham
Professor of Biochemistry and Cell Biology
Rice University

The NSCORT funded research in Dr. Beckingham's laboratory is centered on using *Drosophila melanogaster* as a model organism for studies of gravitational effects on development and behavior. The intensive genetic, developmental and behavioral studies performed in this organism make it ideal for a dissection of the effects of gravity upon these processes. Gravitational effects on two aspects of *Drosophila* biology and physiology are being pursued as described below.

1) Use of a climb assay to identify mutants in a gravitational response

One of the well-characterized behavioral responses of *Drosophila* involves sensing the vector of the gravitational force. Thus, when adult *Drosophila* are tapped to the bottom of a glass vial, they respond by quickly climbing up the vial walls in the opposite direction to the gravitational vector (the "climb" test- see reference 1). This response occurs in the absence of light and other stimuli, indicating that it is purely a response to the direction of the gravitational force. We are using this assay in combination random mutagenesis of the organism (by chemical mutagens) to isolate mutants defective in this test. This will ultimately lead to identification of the genes that mediate the gravitational response. Secondary testing of all mutants identified in this first screen is being performed to eliminate individuals with simple motor defects that interfere with their ability to respond to gravity. For example, mutations that prevent flies from walking properly are being eliminated by this secondary screening step. The small size of *Drosophila*, the simplicity of the screening test and the use of a so-called F1 screening protocol are allowing us to screen very large numbers of potential mutants. To date ~10,000 flies have been examined and at least one potential mutation has been identified.

Our laboratory has considerable expertize and experience in analyzing the effects of mutations to the single calmodulin gene of *Drosophila* (2). Calmodulin is a major intracellular signalling molecule that is known to be involved in Ca^{2+} regulation of many neurophysiological processes (for review see reference 3). We have already demonstrated that mutations to the calmodulin gene fail the climb test even though they appear to walk normally (2). Thus calmodulin may mediate some aspects of this gravitational response. Initially therefore our mutant screening is focussed on identifying mutations that fail the climb test when combined with a weak mutation at the calmodulin gene. Mutations thus uncovered should therefore include those that affect interacting loci. This route will therefore give us access to the genes for additional members of signalling pathway involved in mediating the gravitational response.

2) Gravitational effects upon Ca^{2+} localization and mobilization in the early embryo.

Data from previous space flights indicates that hypogravity has an effect upon the early events of embryogenesis in *Drosophila* (4). Early embryonic development in *Drosophila* is characterized by many rounds of synchronized nuclear replication that occur

in the absence of cytoplasmic division. These divisions are amongst the most rapid known (occurring every 10 minutes) and generate an embryo that is a syncytium with approximately 5000 nuclei in a single cytoplasm. Direct observation has shown that the synchronization of these divisions has a wave-like property. Divisions are initiated at the anterior end of the embryo and an initiation wave spreads along the length of the embryo over a period of many seconds.

Ca^{2+} is known to play a major role in synchronizing mitotic events in other organisms (for examples, see reference 5) and thus one interpretation of the synchronization wave is that it represents a front of Ca^{2+} release from intracellular stores along the length of the embryo. In other systems, release of intracellular Ca^{2+} is also known to be one of the immediate responses to mechanical stress (for example, reference 6). Given that many of the effects of hypogravity reflect perception of altered mechanical forces, our working hypothesis is that the embryonic defects produced in *Drosophila* by hypogravity may involve altered Ca^{2+} movement and mobilization in the early embryo. We have therefore initiated experiments to visualize Ca^{2+} localization and movement in the early embryo both under normal and altered gravitational forces.

Ca^{2+} is being imaged using confocal microscopy and various commercially-available fluorescent calcium sensors. Initial studies have focussed on identifying the best calcium sensor for this work. Although Fluo-3 appears adequate, Calcium-green-dextran has the advantage that it is relatively immobile and thus can be used to monitor changes in a very discrete subregion of the embryo. Thus microinjection of Calcium-green-dextran is currently being pursued.

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PROJECT II

"The Role of Gravity in the Development and Function of the Drosophila Nervous System"

Michael Stern
Assistant Professor of Biochemistry and Cell Biology
Rice University

Specific Aims

The following specific aims were proposed for this project: a) effects of gravity on establishment of neuronal identity; b) effects of gravity on axon pathfinding; and c) effects of gravity on synaptic function. These specific aims have not been modified from the original application. We have begun to perform experiments for each specific aim listed. These experiments are described below:

RESULTS

Overview

Several previous reports suggested that exposure of a developing organism to altered gravity, either micro gravity or hyper gravity, could perturb development or function of the nervous system in subtle but specific ways. These perturbations caused changes in the behavior of the organism at the adult stage, which were observed even after return to normal gravity. The behavioral changes observed were most consistent with abnormalities in the vestibular system, which enables the organism to orient itself properly in space. These effects of altered gravity on the nervous system might be important factors in considering space flights of long duration. Thus it is of interest to define these effects in more detail, and to try to elucidate the cellular and molecular mechanisms by which these effects are generated.

Experimental Protocol

A large number of wildtype Drosophila females lay eggs for a three hour period in six-well micro-titer plates. Two different experimental protocols are then performed: First, the eggs are spun for approximately 15 hours in a low speed centrifuge at 8g of acceleration. After this regimen of experimentation, the developing embryos have completed nervous system development and differentiation. Second, prior to the spin, the eggs are allowed to develop in their micro-titer plates for a variable period of time (0-9 hours), then are spun for three hours , and finally allowed to develop further for a variable period of time (0-9 hours). The first experimental protocol enables a determination of the global sensitivity of the developing embryo to hyper gravity, whereas the second experimental protocol enables the determination of the developmental stage at which this sensitivity to hyper gravity occurs.

Following this treatment, the developing embryos are subjected to one of three further treatments. A first set of embryos are collected, fixed, stained with one of a variety of antibody probes, and then dissected to enable visualization of neuronal structures in both the peripheral and central nervous systems. A second set of embryos are grown to the third instar larval stage, and then assayed for synaptic transmission at the neuromuscular junction with the larval neuromuscular preparation, developed by Jan and Jan in 1976. A third set of embryos are grown to adults, and assayed for behavioral abnormalities,

including altered sensitivity to mechanical force, which might be a phenotype resulting from defects in adult sensory structures.

Preliminary Data Obtained and Plans for the Coming Year

Structure of the central and peripheral nervous system in late stage embryos was determined following two spinning protocols: first, embryos that were spun from 3-6 hours post fertilization, and then those that were spun from 2-17 hours post fertilization. Following these spins, embryos were stained with monoclonal antibody 22C10, which recognizes the cell bodies, axons and dendrites of all neurons, and then dissected to enable visualization. Both the CNS and PNS look normal at this level of analysis. The number of neurons, their positions along the embryo, and the number and positions of nerve cords between the PNS and CNS appear to be normal in spun embryos. These results were anticipated. Previous studies on other vertebrate and invertebrate organisms suggested that the effects of altered gravity on nervous system development would be subtle. If we can confirm that our various spinning protocols have no observable effect on the structure of the CNS or PNS, as assayed by antibody 22C10, we will use other available antibodies that enable the visualization of subclasses of neurons and axons. One antibody of particular interest is 49C3 which specifically recognizes chordotonal neurons and their processes. Such antibodies will allow us to test for more subtle effects of altered gravity on the nervous system, as described in the project description.

Effects of hyper gravity on synaptic transmission at the larval neuromuscular junction were also tested. In particular, we measured the amount of both spontaneous and evoked neurotransmitter release from the larval motor nerve terminal from larvae developed from embryos spun from 3-6 hours after fertilization. We found that all parameters measured for neurotransmitter release appear normal, demonstrating that the three hour spin we induced produced no gross defects in synaptogenesis, synaptic vesicle metabolism or docking, or muscle properties. Additional experiments using spins of longer duration, and possibly at higher g-force, will be performed.

Behavioral data has been obtained from adults arising from embryos that were spun at 3-6 hours post fertilization, 9-12 hours post-fertilization, and 12-15 hours post-fertilization. Although numbers of flies tested are not yet large enough for firm conclusions, it seems unlikely that we will find any significant effect of the three centrifugation protocols tested on the climbing, flight, or sensitivity to mechanical force in flies. These results were also anticipated; because during pupation, the central nervous system of Drosophila is remodeled extensively and the peripheral nervous system is remodeled completely, it seemed unlikely that exposure of developing embryos to hyper gravity would affect behavior in the adult. In this regard, we are planning to investigate the effects of hyper gravity during embryogenesis on behavior of first and third instar larvae. My lab has not performed behavioral studies on Drosophila larvae. However, Dr. Kate Beckingham, who is a member of the Rice Biochemistry department and is a co-investigator in this NSCORT program, has extensive experience in these analyses and has agreed to assist us in these experiments.

PROJECT III

"Molecular and Developmental Responses of Plants to Mechanical Stimuli"

Janet Braam
Associate Professor of Biochemistry and Cell Biology
Rice University

Specific Aims

The major focus of this work is to determine the *in vitro* and *in vivo* functions of the calmodulin-related *TCH2* gene product of *Arabidopsis thaliana*. Expression of *TCH2* is strongly and rapidly upregulated by stimuli such as wind, temperature stress and darkness; thus, *TCH2* may function in the adaptation of plants to environmental stresses. The specific aims of this work (unchanged from the original application) are as follows:

1. Tissue and subcellular localization of TCH2.
2. *In vitro* activity of TCH2.
3. Physiological functions of TCH2.

Results and Plans for the Coming Year

To probe the localization of TCH2 protein in plants, we have generated TCH2-specific antibodies. TCH2 (with a T7 tag) was produced in *E. coli* cells and then partially purified with phenylsepharose chromatography. The antigen was injected into rabbits and antisera were obtained; IgG fractions were isolated by chromatography. One lot of antibodies shows a specific interaction with a single band of the appropriate size of TCH2 on western blots of total plant protein. This band is most likely TCH2 because the protein shifts size in the presence of Ca^{2+} (a characteristic of calmodulin-like proteins) and because the antibody does not recognize purified calmodulin. The antigenic band also increases in abundance in plants exposed to darkness, a stimulus known to increase *TCH2* transcript levels. Thus, we are now poised to begin western analyses of the accumulation of TCH2 protein during development and in plants exposed to various environmental stimuli. These antibodies will enable us to determine the cell and tissue localization of TCH2 protein using light microscopy and to identify the subcellular localization using immuno-electron microscopy.

The second specific aim is to characterize the *in vitro* activity of TCH2. Currently, we are attempting to produce in E. coli "native" TCH2 protein (i.e., lacking any sequence modifications from TCH2 protein produced in plant cells). This protein will be purified by phenylsepharose and then will be used in assays to determine if TCH2 can modulate the activity of known calmodulin targets. In this way, we will learn the significance of the sequence divergence between TCH2 and calmodulin. Furthermore, because we predict that TCH2 is likely to have at least some target proteins unique for TCH2, we will directly screen for TCH2-interacting proteins. We are generating TCH2 with a glutathione-S-transferase tag so that it can be linked to a column resin and used to "pull out" potential target proteins from plant extracts. We will also label this TCH2 protein and use it in gel-overlay assays to look for proteins to which TCH2 binds in a Ca^{2+}-dependent manner. This approach will then also be used to screen cDNA expression libraries so that the genes encoding TCH2-interacting proteins can be isolated and identified.

The analyses described above lead into our overall goal of this work which is to determine the cellular functions of TCH2. One direct approach is to identify plants that are altered in their expression of TCH2. We are using PCR to screen pools of DNA from

plants that have suffered random insertions of T-DNA to determine if any lines harbor T-DNA insertions within the *TCH2* gene. Any such plants would be extremely valuable tools in characterizing the physiological function of TCH2. Furthermore, we have generated plants that have been designed to produce TCH2 antisense and sense transcripts so as to lead to underexpression and overexpression, respectively, of TCH2. Currently, these plants are being analyzed by western blots to determine the effects on TCH2 protein accumulation. Plants that are most dramatically altered in TCH2 protein levels will be thoroughly analyzed for changes in morphogenesis and in molecular and developmental responses to environmental stimuli.

We have discovered through related work in the laboratory that TCH2 expression may be turned on strongly in guard cells during the process of stomatal closure. This response is known to be influenced by cytosolic Ca^{2+} levels and by the ABI-1 protein phosphatase. It is possible, therefore, that TCH2 may function in the process of turgor loss in guard cells. To test this possibility, we will determine (i) whether TCH2 can directly bind ABI-1 using the gel overlay assays described above and the yeast two-hybrid screen and (ii) whether TCH2 can influence guard cell ion channel activity in collaboration with Julian Schroeder's laboratory. We will provide them with antibodies and TCH2 protein to determine if the loss or gain of TCH2 availability in guard cells affects channel activity. In addition, when antisense and sense plants have been sufficiently characterized, the Schroeder laboratory will determine if channel activity in the guard cells from these plants are significantly affected.

PROJECT IV

"Pressure-sensing MAP Kinase Cascades in Yeast and Mammals"

Michael Gustin
Associate Professor of Biochemistry and Cell Biology
Rice University

Two NSCORT research projects have been initiated: (a) molecular analyses of pressure-sensing proteins in yeast, and (b) pressure-sensing MAP kinase pathways in osteoblasts. Research on the yeast pressure sensor project was begun in July 1996 by NSCORT postdoctoral fellow, Dr. Jacobus Albertyn, with help from junior undergraduate, Shion Hung. In May 1996, research on the osteoblast project was begun by second-year graduate student Chris Helmke, with help from senior undergraduate Jonathan Yang, all in collaboration with the NSCORT-funded research group of Dr. Anthony Mikos, Department of Chemical Engineering, Rice University.

Molecular Analyses of Pressure-Sensing Proteins in Yeast

The yeast Saccharomyces cerevisiae responds to changes in external osmolarity by activating or deactivating one of several pressure sensors in its plasma membrane. To determine how a pressure sensor works, we have chosen the Sho1 sensor for structure-function analysis. The goal is to determine which portions of this membrane protein are necessary and sufficient to sense pressure. Our original proposal proposed similar studies of a different sensor called Sln1. Both Sln1 and Sho1 act as osmosensors for the HOG1 MAP kinase pathway, a protein kinase cascade needed for growth at high osmolarity. Mutant analysis show that either Sln1 or Sho1 is sufficient for sensing osmotic changes. The switch of our emphasis to Sho1 was made because (a) the latter protein seems to sense pressure by a novel mechanism, (b) Sho1 is the only pressure sensor known to be activated by a loss of pressure, a physiological stimulus more relevant to the sensing of the microgravity state. Starting from its cytoplasmic NH2 terminus, Sho1 is predicted to have four transmembrane domains followed by a large cytoplasmic domain containing a juxtamembrane region of unknown function and a more COOH-terminal SH3-type region that interacts with a proline-rich domain in the osmosensing MAP kinase kinase Pbs2. Three models for pressure sensing have been proposed. A sensor could sense pressure of extracellular materials on the plasma membrane, stretching of the plasma membrane lipid bilayer, or stretching of the cytoskeleton. There is very little of Sho1 exposed on the outside of the plasma membrane, thus ruling out the former. Thus, Dr. Albertyn has begun making deletions in different portions of Sho1 - transmembrane or cytoplasmic domains - to determine which regions are required for osmosensing. These mutant Sho1 will be tested for function using a yeast strain lacking the SSK2/SSK22 genes that cannot receive a signal from Sln1 and are therefore dependent upon Sho1 for growth in high osmolarity medium.

Pressure-Sensing MAP Kinase Pathways in Osteoblasts

The function of bone-forming osteoblast cells is enhanced by compression on bone. The mechanism by which compression forces activate osteoblast function is currently unknown, but is likely to involve cytosolic signaling pathways that mediate compression-induced changes in bone cell gene expression. One of the most common mechanisms for mediating extracellular signal-induced gene expression is a MAP kinase pathway, of which there are several known in mammals (e.g., ERK, JNK, p38(HOG)). To investigate this

possibility, Chris Helmke and Jonathan Yang have begun an inventory of the MAP kinase pathways present in osteoblasts. With commercially-available antibodies specific for individual MAP kinases, they showed by Western blot analysis that Erk2 and p38 MAP kinases are present in short-term osteoblast cultures taken from rat femurs. Chris has also shown that p38 mRNA is present in mouse osteoblasts by RT-PCR/DNA sequencing. More studies are planned to look at the amount of different MAP kinases present at the different stages - proliferative, matrix synthesis, calcification - of primary osteoblast culture development in vitro. To classify the stage of the culture, the levels of different stage-specific mRNAs will be measured. These studies will be performed in both 2-D and 3-D cultures. For the latter cultures, we will work together with Dr. Mikos's group. Using different biodegradable polymers, they have developed a system for 3-D culture of primary osteoblasts. Following the inventory of MAP kinases, we will then analyze the effect of compression -using a Vitrodyne apparatus - on the 3-D osteoblast cultures, measuring changes in MAP kinase phosphorylation using specific antibodies and changes in stage-specific mRNAs using Northern blots or quantitative RT-PCR. These latter studies we anticipate starting in the coming year.

PROJECT V

"Laminar Fluid Flow Effects on Mammalian Cell Protein Synthesis and Secretion"

Larry V. McIntire
E.D. Butcher Professor of Biomedical Engineering
Rice University

Background

Contrary to the previous belief that a microgravity environment would not affect living organisms at the cellular level, recent findings from the STS-8, SL-1, SL-3 and D-1 missions demonstrate that many cell functions may be altered during spaceflight. These include increases in growth, changes in size, altered DNA transfer during conjugation, aging modifications, and changes in development and cell differentiation. Specific effects on mammalian cells include a 40-50% increase in kidney cell attachment to microcarriers and a five-fold increase in interferon production by *in vitro* lymphocytes, while lymphocyte mitogenic responses are reduced by more than 90%. Even though prolactin secretion remains unchanged, growth hormone release from pituitary cells is decreased. Mechanisms for these changes are not understood.

A consistent problem with much of this work has been the lack of control of many physical and chemical variables and possible nonuniformities in field variables (particularly concentrations). Because of the ability to provide a uniform controlled environment, a stirred-tank bioreactor designed for culture of cells on microcarriers would be ideal for these experiments. However, high agitation rates create hydrodynamic shear and turbulent collisions that result in cell damage and limit the use of fragile cells. Studies on confluent cells in laminar flow chambers have shown that low level fluid shear stress can also alter cell morphology and metabolism, including several-fold stimulation of cell secretion rates. Microgravity experiments need to consider the effects of the hydrodynamic environment within the culture system.

We have chosen as a model cell type the human aortic vascular smooth muscle cell. Recent modeling studies [1] have shown that hASMC normally experience shear stresses in the range of 1-10 dyne/cm^2 due to transmural wall flux. Space flight alters pressure distributions within the vasculature, and therefore alters pressure driven transmural wall flux of fluid. If there are significant effects of fluid stress on SMC metabolism and gene regulation, these may be crucial in modulating vascular remodeling during long term space flight.

Initial Results

Our first studies were to determine the effects of shear stress on nitric oxide (NO) production by cultured human aortic smooth muscle cells exposed to increasing levels of shear stress using parallel plate flow chambers. NO in the conditioned media was assayed fluorometrically by measuring nitrite, a metabolite of NO. Shear stress significantly increased nitrite production and decreased smooth muscle cell proliferation compared to stationary control cultures. An initial rapid increase in nitrite production rate was followed by a more gradual rate of increase throughout the duration of shear stress exposure. Neither the initial rapid nor the prolonged sustained nitrite production was dependent on the level of shear stress in the range 5-25 dyne/cm^2. Repeated exposure to 25 dyne/cm^2 shear stress after a 30 min static period re-stimulated nitrite production similar to the initial burst. BAPTA-AM, a Ca^{++} chelator, blocked shear stress-induced nitrite production, suggesting

that NO production was Ca++ was dependent. N^G-amino-L-arginine, a competitive inhibitor of nitric oxide synthases, blocked nitrite production but not the decrease in cell proliferation rate. Treatment with dexamethasone or cycloheximide had no effect on nitrite production. Monoclonal antibodies directed against the inducible and endothelial nitric oxide synthase isoforms showed no immunoreactivity on Western blots, while monoclonal antibodies directed against the neuronal nitric oxide synthase isoform gave specific products in all control and shear stressed samples. These findings suggest that human aortic smooth muscle cells express a constitutive neuronal nitric oxide synthase isoform, the enzymatic activity of which is strongly modulated by flow-induced shear stress. This work has recently been accepted for publication in *Circulation Research* [2].

To determine whether shear stress regulates gene expression in vascular smooth muscle cells, we investigated the effect of flow on the expression of the human thrombin receptor (HTR) and tissue plasminogen activator (tPA). HASMC were subjected to physiologic levels of shear stress (5-25 dyne/$cm^{2)}$ using parallel plate flow chambers. At different time points (2-24 hours), mRNA levels of HTR and tPA were determined using RNAse protection assays. HTR mRNA was transiently upregulated by 2.1 fold at 5 dyne/cm^2 , while at 25 dyne/cm^2 HTR mRNA decreased at all time points. In contrast, tPA mRNA decreased at 5 dyne/cm^2 after a lag and was upregulated at 25 dyne/cm^2. To further characterize the observed regulation of HTR expression by shear stress, a panel of HTR promoter/luciferase constructs were transfected into rat ASMC and the effect of shear stress on reporter gene expression was examined. The activity of the full length HTR promoter was downregulated by high shear stress (2.5 fold) and a region of the HTR promoter (-160 to -300 bp) was found to be required for shear stress mediated HTR downregulation. These data indicate that shear stress is capable of regulating gene expression in HASMC and that the HTR promoter contains a shear stress sensitive element. This work has recently been submitted for publication [3].

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PROJECT VI

"Regulation of G1 Cyclins and their Cyclin-Dependent Kinases during T Cell Activation in Hypogravity Culture"

Clarence F. Sams, Ph.D. and Joseph E. Penkala, Ph.D.
Research Biochemist, Biomedical Operations and Research Branch
NASA, Johnson Space Center

Background

Studies of lymphocyte (T cell) activation during space flight and in simulated microgravity (clinorotation) show a dramatic reduction of DNA synthesis in response to mitogenic lectins (Cogoli, 1993). While some progress has been made in identifying T-cell inhibition in microgravity, a mechanistic understanding of the inhibition is still lacking. Recently, our laboratory has defined two distinct arrest points for T-cells activated in clinorotation. Specifically, when these cells are activated by lectins or soluble monoclonal antibodies (mAb), they fail to express cell surface activation markers or to secrete lymphokines, indicating a G0 to G1 block. When purified T-cells are activated in clinorotation by phorbol ester (PMA) together with ionomycin (I) or by bead immobilized mAb, they progress into late G1 as evidenced by expression of the receptors for IL-2 and transferrin, and secretion of IL-2. The interaction of IL-2 with its receptor is considered essential for progression through the cell cycle from G1 into S phase (Pauza et al., 1984). In hypogravity inhibition of lymphocytes, the interaction of IL-2 with its receptor, does take place. However, the cells do not exit G1 and fail to initiate DNA synthesis. This finding suggests that hypogravity may alter the regulation of the G1/S checkpoint.

Experimental Design

To elucidate the role of these G1/S regulatory elements in mediating the gravity sensitivity of activated T cells, purified T lymphocytes will be activated with bead bound anti-CD3 or PMA/I and cultured under static (1g) or clinostat (simulated microgravity) conditions. The expression and activity of the G1 cyclins and their cyclin-dependent kinases will then be determined.

A. G1 cyclins and cdks.

1. Expression and assembly of cdk/cyclin complexes. Expression of G1 cyclins A, D2, D3, and E as well as associated kinase subunits, cdk2 and cdk4 will be examinedusing immunoblot analysis with specific antibody probes. Complex formation between specific cyclins and cdks will be determined by immunoprecipitation with anti-cyclin affinity beads, followed by immunoblot analysis of the precipitates and supernatants with anti-cdk antibodies.

2. Activation of cdk/cyclin kinase activity. Since both p33cdk2/cyclin E and p33cdk2 /cyclin A are well characterized and have been identified as key regulators of the G1/S checkpoint, their activation and regulation can be readily examined. Activation of the enzymatic activity of cdk2 kinase will be determined by immunoprecipitation with anti-cyclin E or anti-cyclin A affinity beads, followed by histone H1 kinase assay of the proteins on the beads. It should be noted that cdk4/cyclin D does not phosphorylate histone H1 in vitro, but can phosphorylate pRB (see below).

3. Activation of cdk2/cyclin complex. The cdk2 kinase/cyclin E or A complex is activated by phosphorylation of Thr160 and dephosphorylation of Thr14 and Tyr15 (Sebastian et al., 1993), similar to what has been demonstrated for cdc2 kinase. Analysis of these modifications will be used to assess the regulation of the cdk2 function. The

changes in phosphorylation state of the p33cdk2 peptide can be detected by changes in mobility on SDS-PAGE followed by immunoblotting. This will be verified by anti-phosphotyrosine immunoblotting or phosphoaminoacid analysis.

B. Phosphorylation of retinoblastoma protein.

Hyperphosphorylation of pRB is linked to G1 exit via its dissociation from the transcription factor E2F. Furthermore, it has been shown that cyclins A, D, and E in complexes with cdk2 and cdk4 can perform this phosphorylation of pRB in vitro. Therefore, pRB phosphorylation will be determined following immunoprecipitation, SDS-PAGE, and anti-pRB immunoblotting. The phosphorylation can be observed as a dramatically retarded mobility of the 110 kD pRB band (Dulic et al., 1994).

C. cdk Inhibitors.

1. Expression of p53. It has been shown that under conditions of DNA damage, the transcription factor p53 mediates G1/S arrest via increased production of the universal inhibitor p21 that directly complexes with and inhibits the cyclin/cdks (Dulic et al., 1994; Kastan et al., 1992). In the lymphocyte system of G1/S arrest, we will determine whether elevated levels of p53 can be detected in microgravity culture by Western blotting of cell lysates with anti-p53 .

2. Expression of p21 and p27. Both p21 and p27 are small, heat stable inhibitors of cdk activity that bind directly to cdk/cyclin complexes. It was recently shown that p27 mediates the TGF-beta induced block to cdk activation in lymphocytes, whereas p21 is down regulated in G1 lymphocytes upon stimulation by IL-2 prior to G1 exit (Firpo et al., 1994). To examine whether microgravity induced alterations inhibit cdk function via one of these inhibitory molecules, lysates will be immunoprecipitated with anti-cyclin D, A, or E and immunoblotted with specific probes for p27 and p21 respectively to determine their levels. In addition, inhibitory activity of the lysates will be determined by incubation with S phase extracts, or active cdk/cyclin complexes, and measurement of subsequent H1 kinase activity following immunoprecipitation of the cdks.

Progress to date

The originally stated objectives (above) were based upon observations using the bead-anti-CD3 and PMA/I activation systems. This system usually resulted in entry to the cell cycle (G0/G1 transition) and subsequent arrest at G1/S. We have observed a variability of the G1/S block using these systems that appears to be dependent upon concentrations utilized for the activators. This variability is apparently due to activator concentrations resulting in overstimulation and cell death (with the PMA/I) or induction of anergy (with the bead-anti-CD3). This was a significant problem when basing S phase progression on tritiated thymidine utilization. This assay will look identical for an S phase block or the death of the cells prior to S phase. Therefore, at this time there is some question whether the arrest at G1/S is valid or is an artifact of cell death or anergy. We will continue our efforts to define the experimental system and to remove any influence of potential artifacts. To this end we are now using bromodeoxyuridine incorporation to assess the % of S phase cells. This assay is performed on the flow cytometer and provides a cell-by-cell analysis of cell cycle position. It also allows elimination of non-viable cells and does not have the potential for artifacts of the tritiated thymidine uptake assay. Upon the further definition of our experimental parameters, we will continue the course of investigation outlined above.

In the event that the G1/S block is determined to be untenable for further study, we will focus our attention on the G0/G1 transition. This block is very consistent using both soluble anti-CD3 antibodies or mitogenic lectins. We originally chose to examine the G1/S transition since more is known about the regulatory elements at this cell cycle control point. However, G0/G1 block wouild allow investigation of the coupling between the initial

signal transduction pathways and cell cycle entry. Investigation of the G0/G1 block will focus on the signaling pathways coupling binding of the T cell receptor (TCR) to changes in nuclear transcription. TCR binding activates protein kinase cascades including the MAP kinase system. The investigation of this protein kinase cascade and it's coupling to cell cycle entry can be performed using experimental techniques similar to those outlined above.

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PROJECT VII

"Mechanical Load Effect on Bone Formation"

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Law Associate Professor of Bioengineering
Rice University

Peggy A. Whitson
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NASA, Johnson Space Center

Specific Aims

The research plan includes creating a versatile three-dimensional (3-D) polymer/cell construct to model bone behavior under specific mechanical environments. This model incorporates the simplicity of an isolated system of osteoblasts (bone forming cells) while preserving the matrix environment allowing the cell-cell and cell-matrix communication expected in real bone. The specific aims of this project are:

1. To create 3-D cultures of primary rat osteoblasts attached on biodegradable polymer scaffolds and to form bone tissue *in vitro*. We will explore the effects of seeding density and foam morphology on osteoblast proliferation, function, and matrix synthesis. We will use the knowledge from these studies to develop culturing protocols for creating our 3-D *in vitro* model with controlled cellularity and bone density; and
2. To investigate with the *in vitro* model the effect of static and cyclical compressive strain exerted on the 3-D polymer/osteoblast cultures for:

a) alkaline phosphatase activity, collagen production and gene expression for osteocalcin, osteonectin, and osteopondin, all of which are extracellular matrix components and contribute to mineralization,
b) secretion of cytokines and growth factors which play important roles in the bone remodeling process, and
c) mineralization and bone formation to understand their adaptation to load conditions.

Accomplishments

Bone formation *in vitro* was investigated by culturing stromal osteoblasts in three-dimensional (3-D), biodegradable poly(DL-lactic-co-glycolic acid) foams. Three polymer foam pore sizes and two different cell seeding densities were examined over a fifty-six day culture period. The polymer foams supported the proliferation of seeded osteoblasts as well as their differentiated function which was demonstrated by high alkaline phosphatase activity and deposition of a mineralized matrix by the cells. Cell number, alkaline phosphatase activity, and mineral deposition increased significantly over time for all the polymer foams. Seeding density was an important parameter for the constructs, but pore size over the 150-710 mm range did not affect cell proliferation or function. This study suggested the feasibility of creating 3-D cultures of primary rat osteoblasts attached on biodegradable polymer scaffolds and forming bone tissue *in vitro*. This study also showed that cell seeding needs to be further investigated for creating cell cultures with controlled cellularity and bone density.

We have begun investigations to study cell seeding into porous polymer scaffolds in order to create a 3-D *in vitro* model that better mimics the *in vivo* load conditions. We have developed a new scaffold design and polymer processing method in an attempt to improve cell seeding. *In vitro* experiments where performed with rat marrow stromal osteoblasts seeded and maintained into the scaffolds. To apply strain to the cells within the scaffolds, a new apparatus was also designed and built, which allows us to treat the scaffolds continuously over a long time period and still support the seeded cells inside the scaffold. Moreover, this apparatus allows us to control the mechanical load on 3-D polymer/cell constructs including the frequency of the stimulating strain, strain range within a cycle, ratio of strain change, and maximum force applied to the construct. We will use this apparatus with the 3-D cell cultures to study mechanical load effects on osteoblast gene expression and bone formation.

Deviations

The collaboration with Dr. Barbara D. Boyan of the University of Texas Health Science Center in San Antonio, unfortunately, did not work out because of the distance between Houston and San Antonio. However, we have been very fortunate to establish a collaboration with Dr. M. Cindy Farach-Carson of the University of Texas Dental Branch at Houston who has agreed to serve as a consultant for this project. Dr. Farach-Carson is an expert in skeletal physiology and is currently also funded by NASA.

Research Plan for Year Two

	1/97 - 6/97	7/97 - 12/97
S.A. 1: Develop Cell Seeding Method	------->	
S.A. 2: Study Gene Expression Under Mechanical Stimulation	-------	------->
S.A. 2: Study Protein Synthesis Under Mechanical Stimulation		---------->

S.A. stands for Specific Aim.

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PROJECT VIII

"Mechanical Loading, Growth Factor Release and Regulation of Skeletal Muscle Mass: A Potential Site for the Application of Microgravity-Induced Muscle Atrophy Countermeasures"

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Background

Understanding microgravity-induced musculoskeletal adaptation, specifically microgravity-induced skeletal muscle atrophy (MISMA) is of critical importance to the future of manned space flight. MISMA, with the consequent loss in muscle mass strength and endurance, is one of the most serious, and potentially dangerous, problems faced by crew members during and after extended space flight. However, the mechanism(s) responsible for the initiation of MISMA are unclear. In contrast, the mechanistic nature of the events leading to muscle hypertrophy are better understood. Increasing the mechanical load on skeletal muscle initiates muscle hypertrophy in both human and animal exercise models, whereas disuse/unloading initiates atrophy. Exercise increases the amount of basic fibroblast growth factor (bFGF) detected in muscle and causes satellite cell proliferation *in vivo*, whereas disuse suppresses satellite cell proliferation. We have previously shown that mechanical loading of muscle during eccentric exercise causes wide-spread sarcolemma wounding and a consequent reduction in wounded myofiber bFGF content *in vivo*. In a related study we also detected a dose-dependent, contraction-induced release of both acidic FGF and basic FGF from the rat myocardium. We suggest that mechanically-induced, wound-mediated release of FGF acts as a transduction mechanism for translating mechanical load into a muscle growth response and that disruption of this mechanism during spaceflight plays a significant role in the initiation of microgravity-induced muscle atrophy.

Progress to Date

During the past 12 months we have completed the preliminary studies outlined in our original proposal utilizing our newly acquired Flexcell Strain Unit (FSU). This work appeared as a research article in the FASEB Journal and is the first study to demonstrate a direct, proportional correlation between the amount of mechanical load applied, the degree of sarcoplasmic wounding inflicted on and the quantity of fibroblast growth factor (FGF) released by differentiated human myotube cultures. In addition, this study demonstrated that the growth response induced by mechanical loading was abolished when the action of FGF, released as a consequence of mechanical loaded-induced sarcolemma wounding was blocked using a specific, site-directed FGF neutralizing antibody. As such, this work directly demonstrates that sarcolemma wound-induced FGF release is a central signaling mechanism involved in mechanical load-induced skeletal muscle growth. We have recently acquired a second FSU culture platform which will be used for the study of **unloading** on human skeletal muscle cells.

A second area of investigation of great importance, although not directly related to the NSCORT study, is the development in this laboratory of an immortalized human skeletal myoblast cell line, Myo5LT, capable of normal terminal differentiation in culture. Access to this cell line will assure a consistent and reliable source of human myocytes and myotubes for use in the planned FSU experiments, without the need to return to the costly and time-consuming isolation of primary human skeletal muscle myocyte cultures from needle biopsy material. These cells (Myo5LT) have been successfully grown as myocytes in collagen-

coated FSU culture plates and will prove indispensable in our future studies on the effects of unloading on human skeletal muscle *in vitro*.

A third research project in this laboratory, a bedrest study completed August 1996, has yielded some very encouraging results which have direct implications for the research being carried out under the auspices of the NSCORT Award. The bedrest study has shown that myofiber wounding is significantly reduced during bedrest, that circulating acidic FGF levels are significantly reduced and that these changes are paralleled by significant skeletal myofiber atrophy of the m. vastus lateralis. When the test subjects underwent a resistive exercise protocol during bedrest, muscle acidic FGF content, myofiber wounding and circulating acidic FGF levels were all significantly increased. These changes were paralleled by prevention of the bedrest-induced myofiber atrophy detected in unexercised bedrest subjects. These results suggest that the central concept of mechanical load-induced, sarcolemma-mediated FGF release as a central signaling pathway in the maintenance of skeletal muscle mass *in vivo* is correct. The program of research for the NSCORT project will further help us to understand the basic molecular mechanisms involved in the unloading response in human skeletal muscle, using the highly reproducible and controllable environment of the FSU.

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PROJECT IX

"Microgravity Effects on Lymphocyte Adhesion and Motility"

Kyriacos Zygourakis
Professor of Chemical Engineering
Rice University

Specific Aims

This project will focus on the effects of microgravity environments on cells of the immune system. Activation of T lymphocytes requires a specific sequence of cell signaling and intracellular events that are triggered through interactions with monocytes or other antigen-presenting cells (APC). Since migration of lymphocytes and their adherence to other cells are two of the most significant properties modulating these interactions, our research will concentrate on elucidating the effect of microgravity environments on the pathways of lymphocyte adhesion and motility. Measurements of lymphocyte aggregation rates and migration speeds will be performed using two sensitive assays based on video microscopy and digital image processing.

Results

During the past six months, we completed the development of a model that describes the kinetics of homotypic cellular aggregation. Such a model is necessary for correctly interpreting the results from lymphocyte aggregation experiments.

The study of cellular aggregation under an optical microscope is a common method used by immunologists to study the role of various reagents in activating and modulating cell adhesion. For a typical aggregation experiment, lymphocyte cells are activated and placed on the bottom of a tissue culture well. As the activated cells move on the well surface and collide with other cells, they form large multi-layered aggregates. For lymphocyte systems, we expect that the rate of aggregation will depend on (a) the rate of collision of cells and cell aggregates, and (b) the ability of the two colliding species to bind upon contact. Collision rates are strong functions of the cell migration speed and the size of the aggregates. In turn, cell migration speed is governed mainly by its cytoskeletal activity. The fraction of cell collisions resulting in adhesion gives the sticking probability which depends on the concentration of surface receptors and their affinities for the ligands on the opposing species. These parameters are affected both by the level of cell activation and by more subtle biological variables such as the cell cycle and cell-surface interactions. They are probably also time-dependent because of activation and down-regulation of adhesion processes.

The above points are sometimes overlooked by investigators analyzing cellular adhesion by monitoring aggregation, and this can lead to misinterpretation of the experimental data. For example, two systems may have similar aggregation kinetics even though they have very different binding capabilities: a system with highly motile cells with low-affinity receptors may be indistinguishable from one with cells having low motility but high affinity receptors. Comparisons among various aggregation experiments are further complicated due to difficulties in controlling other system parameters such as the initial cell density.

To resolve these problems, we have developed a kinetic model and applied it to the analysis of experimental aggregation data. The model considers cellular aggregation under no-flow conditions as a two-step process. Individual cells and cell aggregates (a) move on the tissue culture surface and (b) collide with other cells (or aggregates). These collisions lead to the formation of intercellular bonds. The aggregation kinetics are described by a

system of coupled, non-linear ordinary differential equations and the collision frequency kernel is derived by extending Smoluchowski's colloidal flocculation theory to cell migration and aggregation on a 2-dimensional surface. To relax some of the restrictive assumptions of earlier models and to more accurately simulate the behavior of our aggregation system, we modified the kinetic kernel in accordance with our experimental findings and basic collision theory principles. Model predictions agree well with data from homotypic lymphocyte aggregation experiments using Jurkat cells activated by 33B6, an antibody to the b_1 integrin. This comparison allowed us to quantify the dependence of aggregation rates on (a) the motility of cells and cell aggregates, (b) the frequency of cell-cell collision and (c) a measure of the strength of inter-cellular bonds. Thus, this model provides a potentially useful tool for identifying the important physiological parameters involved in aggregation and for correctly interpreting experimental data obtained from visual assays of homotypic cellular aggregation. The usefulness of our model is enhanced by the fact that cell migration speeds and all the other model parameters can be independently measured.

Plans for the Coming Year

We plan to extend our studies on lymphocyte aggregation and motility to cells that have been cultured in a simulated microgravity environment. The cells will be stimulated with monoclonal antibodies to the b_1 integrin (33B6 and 18D3) and cultured in clinostats either in suspension or encapsulated in gel matrices for varying periods of time. After removing them from the clinostat, the lymphocyte adhesive properties and motility will be assayed at several time points. Homotypic aggregation kinetics will be measured using our novel assay and receptor expression levels will be quantified using flow cytometry. We will also study the energetics of receptor activation by examining the effects of temperature and various chemical stimuli (phorbol ester, cytochalasin B) on the activation epitope expression and on the homotypic activation function. Finally, the level of cell activation will be quantified using flow cytometry to monitor changes in intracellular Ca^{+2} levels. These studies will address the following questions: (A) Does exposure to simulated microgravity affect the receptor expression and the binding of monoclonal antibodies to corresponding epitopes of the b_1 integrin ? (B) Does simulated microgravity affect the aggregation kinetics and do we observe any dosage-dependence effects that can be used to control this adhesive function ? (C) Is cell avidity altered only due to conformational changes of the b_1 integrin or does ligand binding induce intracellular activation signals that modulate lymphocyte adhesion function ?

Using a second assay we developed, we will also evaluate the motility of lymphocytes exposed to simulated microgravity by measuring their speed of locomotion, persistence of movement and turn angle distribution. The lymphocytes will be activated with 33B6 and 18D3 mAbs before and after clinostat exposure. Surfaces coated with varying concentration of extracellular-matrix proteins (like fibronectin) will be used for the motility measurements.

Student Training

A new Ph.D. student (Art Bergman) has started working on this project and he will carry out the lymphocyte aggregation and motility experiments in the coming year. A Rice undergraduate student (Matthew Wong) has also worked on this project last summer (June 1- August 15, 1996) carrying out cell motility measurements and implementing a new image analysis technique for measuring changes in the shape and size of migrating cells.

References

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EDUCATION, TRAINING AND OUTREACH

Our NSCORT education, training and outreach activities are reported in accordance with the following definitions set forth by the NASA Space Life Sciences Division, Office of Life and Microgravity Sciences and Applications:

Training - Learning opportunities and information dissemination designed primarily for NSCORT members and staff.
Education - Education information or activities designed for grades K-14 that benefit students other than NSCORT trainees, and participation by NSCORT members in professional association conferences, etc.
Outreach - Activities that extend NSCORT information to business and general public audiences.

A. TRAINING

Students in Training

During the first year of our NSCORT in Gravitational Biology 22 students have received training (4 postdoctoral; 7 graduate students; and 11 undergraduates) in the laboratories of our NSCORT investigators. In addition to these research experiences, the NSCORT-affiliated postdoctoral fellows and students (both graduate and undergraduate), along with all students and postdocs affiliated with the Institute of Biosciences and Bioengineering are encouraged to attend both the Biweekly and Monthly NSCORT Seminars described below under Training Opportunities.

NSCORT Postdoctoral Fellows, Graduate Students and Undergraduates

Name	Dates of Appointment	Training Received in the Laboratory of:
4 Postdoctoral Fellows:		
Keith Johnson	Mar 1, 1996 - Feb 28, 1997	J. Braam
Jacobus Albertyn	Jul 2, 1996 - Feb 28, 1997	M. Gustin
Markus Widmer	Jun 1, 1996 - Feb 28, 1997	T. Mikos and P. Whitson
Heidi Nelson	Aug 1, 1996 - Feb 28, 1997	K. Beckingham
7 Graduate Students:		
LaChelle Warbington	Mar 1, 1996 - Feb 28, 1997	M. Stern
Stephen Richards	Mar 1, 1996 - Aug 31, 1996	M. Stern and K. Beckingham
Christopher Helmke	May 16, 1996 - Feb 28, 1997	M. Gustin
David Rhoads	May 16, 1996 - Feb 28, 1997	L. McIntire
Rob Thomson	Jul 1, 1996 - Feb 28, 1997	T. Mikos and P. Whitson
Arthur Bergman	Apr 1, 1996 - Feb 28, 1997	K. Zygourakis
Suzie Ishaug	Mar 1, 1996 - Jun 30, 1996	T. Mikos and P. Whitson
11 Undergraduate Students:		
Monica Ramos	Aug 26, 1996 - Feb 28, 1997	J. Braam
Kasia Mucha	May 16, 1996 - Aug 15, 1996	K. Beckingham
Susan Lang (1/2 time)	May 16, 1996 - Aug 15, 1996	M. Stern
Andrew Varga (1/2 time)	Jun 3, 1996 - Aug 15, 1996	M. Stern
Jasper Liu	May 16, 1996 - Aug 15, 1996	J. Braam

Daniel Lin	May 16, 1996 - Aug 15, 1996	M. Gustin
Jessica Nolley	May 16, 1996 - Aug 15, 1996	T. Mikos and P. Whitson
Matthew Sing Wong	May 16, 1996 - Aug 15, 1996	K. Zygourakis
Toma Miller	Sept 9, 1996 - Feb 28, 1997	J. Braam
Liang Wang	Sept 11, 1996 - Feb 28, 1997	K. Beckingham
Allyson Woods	Sept 25, 1996 - Feb 28, 1997	K. Beckingham

NASA-NSF-GRC Award

Dr. Keith Johnson, NSCORT Postdoctoral Fellow in the laboratory of investigator Janet Braam, was awarded a NASA-NSF-GRC Young Investigator Stipend to attend the Gordon Conference on "Gravitational Effects on Living Systems" held at Colby-Sawyer College, New London, New Hampshire, July 14-19, 1996. Dr. Johnson presented an abstract and poster at the meeting, which is reported below under the category of Professional Education.

Training Opportunities

Biweekly Seminar Series

A Biweekly Seminar series has been initiated. The seminars are for NSCORT faculty to present detailed presentations of their research projects. All faculty, postdocs and students affiliated with the NSCORT and with the Institute of Biosciences and Bioengineering are invited to attend these seminars. At this reporting, the two most recent seminars to be presented (including the Thanksgiving holiday) were:

Friday, November 8
Presenting: Dr. Michael Stern and Graduate Student LaChelle Warbington
Title of Talk: "Effects of Altered Gravity on the Development and Function of the Nervous System of Drosophila melanogaster."

Friday, December 13
Presenting: Dr. Michael Gustin
Title of Talk: "Pressure-Related Signaling Pathways in Large and Small Creatures - A Tale of Bones and Beer"

Monthly Seminar Series

Our most recent NSCORT Monthly Seminar was held on Wednesday, December 11, 1996. This seminar series is designed to bring outside speakers to the campus whose research interests are relevant to the Rice NSCORT research projects. These monthly seminars are open to NSCORT members, the Rice campus community (including all faculty, postdoctoral fellows, graduate students and undergraduates affiliated with the Institute of Biosciences and Bioengineering), and the general public. The site for these seminars alternates between Rice University and the Johnson Space Center.

Wednesday, December 11
Presenting: Dr. Karl H. Hasenstein, Associate Professor of Biology , University of Southwestern Louisiana
Title of Talk: "Induction of Plant Curvature by Magnetophoresis and Cytoskeletal Changes During Root Graviresponse."

Graduate and Undergraduate Courses

Graduate and undergraduate courses are being developed. These will be space technology related courses which will be new additions to the biological sciences curriculum at Rice and will consist of two offerings - a broad course in space technology with emphasis on effects of microgravity on biological systems and a second course taught as an upper division course dealing with specific aspects of current research in this area. The first course will be open to all students with minimal prerequisites. These courses will utilize Johnson Space Center personnel to a large degree. This will provide a major opportunity for NASA to interact with university students, including those not involved directly in this program, who have strong interests in space activities.

Visit by Morehouse School of Medicine Investigators

On December 11, eighteen scientists affiliated with the Morehouse School of Medicine Space Life Science Center visited Rice to meet with Rice NSCORT faculty to learn about our NSCORT and to establish a connection between our two centers. Director Larry McIntire presented an overview of the Rice NSCORT, followed by an overview by Dr. C. Sanborn of the research activities of the Morehouse Space Life Science Center. A question and answer period was followed by informal discussions among the two groups of investigators.

Attendance at Professional Conferences

This year six NSCORT faculty and students attended professional conferences directly relating to gravitational biology.

Annual ASGSB Meeting in Washington D.C., October 25-29, 1995
- Attended by NSCORT Associate Director Frederick B. Rudolph and NSCORT Investigator Dr. Janet Braam

1996 Summer Gordon Conference entitled "Gravitational Effects on Living Systems", Colby-Sawyer College, July 14-19, 1996
- Attended by NSCORT Investigator Dr. Kyriacos Zygourakis and NSCORT Postdoctoral Fellow Dr. Keith Johnson

1996 Annual ASGSB Meeting in Charlotte, North Carolina, October 23-26, 1996.
- Attended by NSCORT Director Larry V. McIntire and NSCORT Investigator Dr. Clarence Sams

B. EDUCATION

Professional

A complete list of Publications, Abstracts and Conference Presentations based on NSCORT research is presented on pages 29-31 of this report.

Education

Development of Rice NSCORT Educational Programs

Several communications with Ms. Bonnie McClain, NASA Life Science Education Programs Coordinator helped us clarify the types of educational activities and programs

that would be best suited to our NSCORT. On December 11, 1996, Ms. McClain visited our NSCORT. The information and advice she provided was extremely useful in helping us focus on specific programs for our NSCORT.

A network of K-12 programs sponsored by the Howard Hughes Medical Institute and administered through the Rice Univeristy Department of Biochemistry and Cell Biology has been in existence since 1990. The Hughes grant currently supports a program for secondary school involvement which exposes all teachers of science in the Houston Independent School District (which has a significant minority population) to advances in the field and acquaints them with modern techniques. The program was developed with an attempt to facilitate recruiting students, while simultaneously providing benefits independent of the specific selection of graduate institution. A clear objective of these K-12 initiatives is to increase enrollment of minority (as well as students in general) in science and engineering, particularly during the high school years.

Our NSCORT educational activities will be integrated into these well established programs. The addition of a NASA component will enhance the attractiveness of the existing programs and integrate all of the initiatives to allow maximum impact on recruitment and training of minority students and students in general in science and engineering.

These activities will be coordinated by Diana Welch, Assistant Director of the Institute of Biosciences and Bioengineering and designated Education Contact Person for our NSCORT. Ms. Welch will continue to consult with Ms. McClain as the Rice NSCORT educational programs are initiated.

C. OUTREACH

Presentations

Annual Symposium

The Rice NSCORT's first Annual Symposium will be held on the Rice campus in Spring 1997. The conference will consist of a keynote lecturer in the area of space biology, talks on current research projects, and will include a poster session. The External Review Committee will meet as a part of this event and provide guidance for operation of the program. The symposium will be advertised locally and nationally and a particular effort will be made to encourage attendance by industrial groups. Local high school and college students and teachers will be invited to this event as a part of outreach activities.

Media

Advertisements

The Rice NSCORT was advertised in the May 24, 1996 issue of *Science* and the September 21, 1995 issue of the *Rice News*.

NSCORT Web Homepage

The Rice NSCORT has been added to the Rice University Institute of Biosciences and Bioengineering's world wide web homepage. The address is http://www-bioc.rice.edu./Institute/IBB.brochure/index.html.

NSCORT Information Materials

Flyer

A general information flyer describing the mission of the Rice NSCORT in Gravitational Biology and the research focus areas was prepared and distributed at both the 1995 and 1996 ASGSB Annual Meetings. A copy of this flyer is attached as Appendix A.

Institute Annual Report

The awarding of the NSCORT to Rice University was reported in the 1995 Annual Report of the Institute of Biosciences and Bioengineering, a copy of which is attached to this report as Appendix B. This publication is mailed to over 2,500 scientific colleagues, business contacts, donors and friends of Rice University and the Institute of Biosciences and Bioengineering.

The 1996 Annual Report of the Institute is in press at this time. This report contains a followup story on the initiation of our NSCORT on March 1, 1996. A copy of this publication will be forwarded to NASA Grant Officer Dr. Barbara Cephas and NASA Technical Officer Ms. Vicki Thorne as soon as it is available.

PUBLICATIONS, ABSTRACTS AND CONFERENCE PRESENTATIONS

Publications Arising From NSCORT Activities:

1. Clarke, M.S.F. and **Feeback, D.L.** (1996) Mechanical load induces sarcoplasmic wounding and FGF release in differentiated skeletal muscle cultures. FASEB J. 4:127-139.
2. L. Lu and **A.G. Mikos** (1996), "The Importance of New Processing Techniques in Tissue Engineering," *MRS Bulletin, 21,* 28-32.
3. A.C. Jen, S.L. Ishaug, M.J. Yaszemski, L.V. McIntire, and **A.G. Mikos,** (1996) "Three Dimensional *In Vitro* Mechanical Model for Bone Formation," *Trans. World Biomater. Congr., 5,* I-979.
4. Richards, S., Hillman, T. and **Stern, M.** (1996) Mutations in the *Drosophila* pushover gene confer increased neuronal excitability and spontaneous synaptic vesicle fusion. *Genetics* 142: 1215-1223.

In Press:

5. Papadaki, M., Tilton, R.G., Eskin, S.G. and **McIntire, L.V.**, "Nitric oxide production by human aortic smooth muscle cells: Modulation by fluid shear stress" *Circulation Research* , accepted for publication (1996).
6. S.L. Ishaug, G.M. Crane, M.J. Miller, A.W. Yasko, M.J. Yaszemski, and **A.G. Mikos,** "Bone Formation by Three-Dimensional Stromal Osteoblast Culture in Biodegradable Polymer Scaffolds," *J. Biomed. Mater. Res.,* in press (1996).
7. S.L. Ishaug-Riley, G.M. Crane, A. Gurlek, M.J. Miller, M.J. Yaszemski, A.J. Yasko, and **A.G. Mikos**, "Ectopic Bone Formation by Marrow Stromal Osteoblast Transplantation Using Poly(DL-Lactic-co-Glycolic Acid) Foams Implanted into the Rat Mesentery," *J. Biomed. Mater. Res.,* in press (1996).
8. S. Neelamegham, L.L. Munn and **K. Zygourakis**, "A Mathematical Model for the Kinetics of Homotypic Cellular Aggregation under Static conditions," *Biophysical Journal*, 72, in press (1997).

Submitted:

9. Nelson, H., Heiman, R.G., Bolduc, C., Kovalick, G.E., Whitley, P., **Stern, M.** and **Beckingham, K.,** Calmodulin point mutations affect *Drosophila* development and behavior. Submitted for publication to *Genes and Development*, (1996).
10. Ruet, J., Papadaki, M., Eskin, S.G., **McIntire, L.V.** and Runge, M.S., "Differential regulation of thrombin receptor and tissue plasminogen activator expression by shear stress in human aortic smooth muscle cells," submitted for publication to *Journal of Clinical Investigation* (1996).
11. Clarke, M.S.F., Candal, F.J., Vanderburg, C.R., Ades, E.W. and **Feeback, D.L.** (1996) Establishment of an immortalized adult human skeletal muscle cell line (Myo5LT) capable of differentiation in tissue culture. Submitted for publication to *Developmental Dynamics* (1996).

Abstracts and Conference Presentations of NSCORT Activities:

1. Johnson, Keith A. and **Braam, Janet** (1996) The TCH2 Gene of Arabidopsis Encodes a Novel Calmodulin-Related Protein: Its Expression Pattern Indicates a

Possible Role in Plant Responses to Mechanical Stimulation. Abstract presented at the 1996 Summer Gordon Conference Conference entitled "Gravitational Effects on Living Systems", Colby-Sawyer College, July 14-19, 1996.

2. **Braam, Janet** (1996) Regulation of Expression and Functions of XET and Calmodulin-Related TCH Genes of Arabidopsis. Symposium on Calcium and Gravitational Biology, November 2, 1996, The North Carolina Biotechnology Center, Research Triangle Park, NC.
3. Bamman, M.M., Clarke, M.S.F., **Feeback,D.L.**, Powers, S.K. and Stevens, B.R. (1996) Myosin heavy chain distribution following bed rest with and without resistance exercise. (Abstract) The American College of Sports Medicine, Denver, CO.
4. Clarke, M.S.F., Bamman, M.M. and **Feeback, D.L.** (1997) Myofiber wound-mediated FGF release and muscle atrophy during bedrest. (Abstract), Experimental Biology '97, New Orleans, LA.
5. **McIntire, L.V.**, Papadaki, M. and Eskin, S.G. (1996). Invited lecture "Flow Modulation of Smooth Muscle Cell Proliferation and Metabolism" Vth Biennial Meeting of the International Society for Applied Cardiovascular Biology, Manchester, England, March, 1996.
6. Papadaki, M. Eskin, S.G., Tilton, R. and **McIntire, L.V.** (1996) "Fluid Shear Stress Increases Nitric Oxide Production by Cultured Human Aortic Smooth Muscle Cells" Experimental Biology '96, Washington, DC, April, 1996.
7. **McIntire, L.V.**, Eskin, S.G. and Papadaki, M. (1996) Invited lecture "Modulation of Gene Expression in Mammalian Cells by Fluid Flow and Mechanical Strain" 5th World Congress of Chemical Engineering, San Diego, California, July, 1996.
8. Eskin, S.G., Tilton, R., Papadaki, M. and **McIntire, L.V.** (1996) "Nitric Oxide Production by Shear Stressed Smooth Muscle Cells" IXth International Vascular Biology Meeting, Seattle, Washington, September, 1996.
9. Runge, M., Papadaki, M., Ruet, J., Eskin, S.G. and **McIntire, L.V.** (1996) "A Novel Effect of Fluid Shear Stress: Down-regulation of Human Thrombin Receptor mRNA and Promoter Activity in Human Aortic Smooth Muscle Cells" American Heart Association - 69th Scientific Sessions, New Orleans, LA, November, 1996.
10. Papadaki, M., Runge, M., Eskin, S.G., and **McIntire, L.V.** (1996) "Thrombin Receptor and Plasminogen Activator mRNA Levels are Modulated by Shear Stress in Human Aortic Smooth Muscle Cells" Annual Meeting of the American Institute of Chemical Engineers, Chicago, IL, November, 1996.
11. G.M. Crane, S.L. Ishaug, M.J. Miller, M.J. Yaszemski, and **A.G. Mikos**, "Three-Dimensional Bone Formation Using Biodegradable Polymer/Stromal Osteoblast Constructs," Keystone Symposium on Tissue Engineering, Taos, New Mexico, January 24, 1996.
12. S.L. Ishaug, G.M. Crane, M.J. Yaszemski, and **A.G. Mikos**, "Three-Dimensional Calvaria Osteoblast Culture in Biodegradable Polymer Scaffolds," 14th Annual Conference of the Houston Society for Engineering in Medicine and Biology, Houston, Texas, February 8, 1996.
13. A.C. Jen, S.L. Ishaug, M.J. Yaszemski, L.V. McIntire, and **A.G. Mikos**, "Three Dimensional *In Vitro* Mechanical Model for Bone Formation," 14th Annual Conference of the Houston Society for Engineering in Medicine and Biology, Houston, Texas, February 8, 1996.
14. S.L. Ishaug, G.M. Crane, M.J. Miller, M.J. Yaszemski, and **A.G. Mikos**, "Bone Formation Using Stromal Osteoblasts Cultured in Biodegradable Polymer Foams," 14th Annual Conference of the Houston Society for Engineering in Medicine and Biology, Houston, Texas, February 8, 1996.
15. G.M. Crane, S.L. Ishaug, M.J. Miller, M.J. Yaszemski, and **A.G. Mikos**, "Three-Dimensional Bone Formation Using Biodegradable Polymer/Stromal

Osteoblast Constructs," 15th Southern Biomedical Engineering Conference, Dayton, Ohio, March 31, 1996.

16. S.L. Ishaug, G.M. Crane, and **A.G. Mikos**, "3-D Osteoblast Culture in Biodegradable Polymer Foams," 5th World Biomaterials Congress, Toronto, Canada, May 30, 1996.
17. A.C. Jen, S.L. Ishaug, M.J. Yaszemski, L.V. McIntire, and **A.G. Mikos,** "Three Dimensional *In Vitro* Mechanical Model for Bone Formation," 5th World Biomaterials Congress, Toronto, Canada, June 2, 1996.
18. S.L. Ishaug, G.M. Crane, M.J. Yaszemski, and **A.G. Mikos**, "Three-Dimensional Osteoblast Migration in Biodegradable Polymer Foams," 5th World Congress of Chemical Engineering, San Diego, California, July 16, 1996.
19. A.C. Jen, **A.G. Mikos**, J. Mayer, and E. Wintermantel, "Biocompatible Fiber-Reinforced Composites for Culturing Osteoblasts," Annual BMES Fall Meeting, State College, Pennsylvania, October 6, 1996.
20. A.C. Jen, J.L. Almaguer, S.D. Cho, M.S. Widmer, **A.G. Mikos**, K. Akanbi, and M.C. Farach-Carson, "Three-Dimensional Polymer/Cell Mechanical Model for Bone Formation," Post-ASME Workshop on Cell Biomechanics, Georgia Institute of Technology, Atlanta, Georgia, November 23, 1996.

Appendices

A. Rice NSCORT Information Flyer

B. 1995 Annual Report of the Rice Institute of Biosciences and Bioengineering

RICE

NASA Specialized Center of Research and Training (NSCORT) in Gravitational Biology

RICE UNIVERSITY
INSTITUTE OF BIOSCIENCES AND BIOENGINEERING

The goal of the NSCORT at Rice University is to develop a high quality training and research program that will establish a NASA-university base for space-related research. The research emphasis will be in the area of Gravitational Biology, in particular the investigation of the effects of gravity and other environmental factors on biological function at the cellular and molecular level. The research efforts, training opportunities, and scientific exchange will promote the expansion of a scientific peer group well-educated in space-related biological issues. This will stimulate the interest of the larger scientific community and insure the continuing development of rigorous flight investigations in Gravitation Biology.

There are twelve major research projects which span a wide range of interests. The model systems have been carefully chosen so that specific mechanistic questions at the cellular and molecular level can be addressed and so that once the proper ground-based data have been assembled, the development of flight based proposals will not be difficult. Brief overviews of the research programs are given, followed by the titles of the included projects and the project principal investigator.

MAJOR RESEARCH PROJECTS

RESPONSES TO MECHANICAL STIMULI

Several of the project principal investigators have established research programs centered on understanding the molecular basis of the response of various cell types to mechanical stimuli. These projects examine basic cellular mechanisms involved in sensing the mechanical force environment, in transduction of these signals, and in gene regulation, using arabidopsis, yeast and mammalian cell models. They interact closely with each other because of their common scientific interest in signal transduction, and the understanding gained forms a mechanistic basis for developing hypotheses concerning the effect of microgravity on cell function. The data produced will also have wide application in many other areas where mechanical forces are intimately coupled with gene regulation and cell metabolism.

- **Molecular and Developmental Responses of Plants to Mechanical Stimuli (Janet Braam)**
- **Pressure-Sensing MAP Kinase Cascades in Yeast and Mammals (Michael Gustin)**
- **Laminar Fluid Flow Effects on Mammalian Cell Protein Synthesis and Secretion (Larry V. McIntire)**

Rice University • Institute of Biosciences and Bioengineering - MS 144 • 6100 South Main Street • Houston, Texas 77005-1892
Phone: (713) 527-6034 • Fax: (713) 285-5154

DEVELOPMENTAL BIOLOGY

Another focus area in the NSCORT is centered on understanding the effect of microgravity and associated stresses on development at the molecular and cellular level. Drosophila are chosen as the model system for these developmental biology projects because of the wealth of molecular level knowledge and reagents that are available to allow testing of very specific mechanistic hypotheses. In addition, this model system is relatively easy to translate to actual flight experiments once ground-based research identifies the proper questions to ask and establishes the requisite data base for comparison.

- **The Role of Gravity in Early Embryonic Pattern Formation**
  (Kate Beckingham)

- **The Role of Gravity in the Development and Function of the Drosophila Nervous System**
  (Michael Stern)

OTHER SYSTEMS

The remaining seven projects examine specific hypotheses focused on understanding the molecular and cellular basis of several documented cellular alterations seen in space flight. These include a dramatic reduction in lymphocyte DNA synthesis in response to mitogens and in migration, increased bone resorption and demineralization, and skeletal muscle atrophy. Finally, two exciting basic research projects on understanding microgravity effects on cytoskeletal assembly in mammalian cells (both in suspension and for attachment-dependent cells) and effects of microgravity on microbe-host interaction will be undertaken.

- **Regulation of G1 Cyclins and their Cyclin-Dependent Kinases During T Cell Activation in Hypogravity Culture**
  (Clarence F. Sams)

- **Microgravity Induced Changes in Lymphocyte Movement Through Interstitium**
  (Neal Pellis)

- **Microgravity Effects on Lymphocyte Adhesion and Motility**
  (Kyriacos Zygourakis)

- **Mechanical Load Effects on Bone Formation**
  (Antonios G. Mikos and Peggy Whitson)

- **Mechanical Loading, Growth Factor Release and Regulation of Skeletal Muscle Mass: A Potential Site for the Application of Microgravity-Induced Muscle Atrophy Countermeasures**
  (Daniel L. Feeback)

- **Hypergravity and Simulated Hypogravity Effects on Cytoskeletal Components of Attachment-Dependent Cells and Suspension Cells**
  (Peggy A. Whitson and Clarence F. Sams)

- **Microgravity: Effects on Microbe-Host Interactions**
  (George Bennett and Frederick Rudolph)

EDUCATION AND TRAINING OPPORTUNITIES

Education and training at the Rice NSCORT involves undergraduates, graduate students and post-doctoral fellows. Increasing the participation of minorities and women at all levels of research and training is a first priority in recruitment.

The research projects of the Rice University Institute of Biosciences and Bioengineer NSCORT in Gravitational Biology represent a wide range of research areas. We hope to attract the highest quality young scientists and engineers as potential trainees.

Training provided under this program will be focused in two areas. Research opportunities will obviously be a major focus. The second focus will involve seminars and space technology related courses. Research programs for undergraduates and new courses are being developed (such as one in Tissue Engineering). Undergraduate research will be emphasized particularly in the research courses offered both in bioengineering and biosciences. Graduate students and post-doctoral fellows will do research in laboratories both at Rice and at NASA-JSC. This exchange of personnel will help in knowledge transfer and help insure close interaction on a daily basis of the project investigators. Outreach and knowledge transfer will be the focus of an annual NSCORT Symposium and Poster retreat. Investigators from other universities, national laboratories and the biotechnology industry will be invited. At the end of the five-year grant period, a major International Symposium on Gravitational Biology will be held in Houston, sponsored by the Institute of Biosciences and Bioengineering and held jointly with NASA-JSC.

Requirements in Graduate Program. This program includes two departmental components, the Department of Biochemistry and Cell Biology and the Department of Chemical Engineering. Students will apply to a selected department and will meet requirements for those specific programs. The primary common ground for the students in these two departments will be the seminar series which includes all students who are in laboratories of faculty participating in the NSCORT training program. These situations in which students are gathered together from various disciplinary contexts will provide a rich setting for education, discussion, insight, and simply getting to know individuals in other laboratories and opportunities for interaction with NASA scientists will add to that experience.

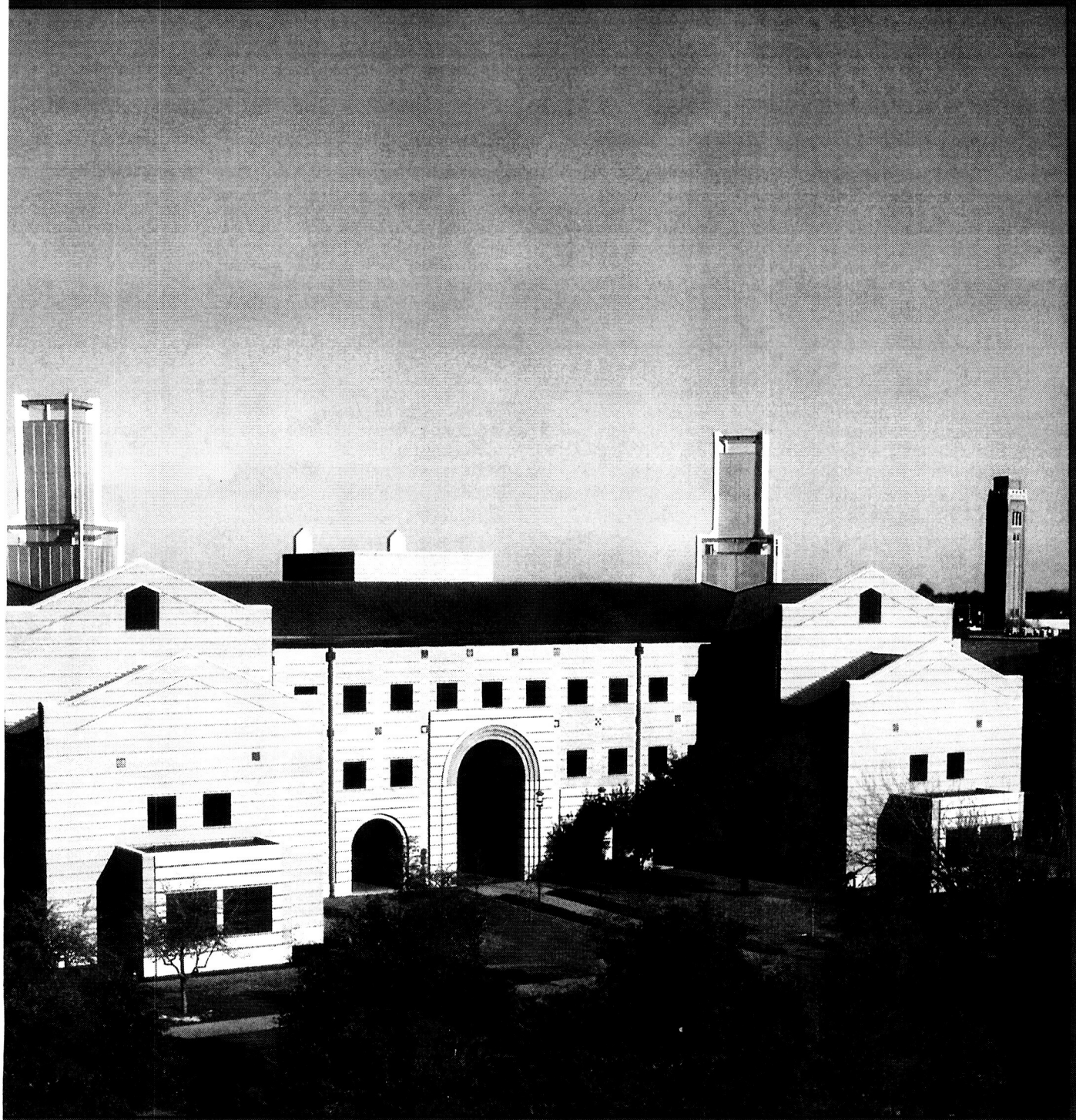
** Postdoctoral Positions Available **

Applications for postdoctoral positions for the Rice University Institute of Biosciences and Bioengineering NSCORT in Gravitational Biology are currently being accepted. For more information, interested candidates as well as others interested in graduate or other research opportunities should contact:

Dr. Frederick B. Rudolph
Institute of Biosciences and Bioengineering
NSCORT Project
Rice University - MS 144
6100 S. Main
Houston, Texas 77018

Phone: (713)527-4015; EMail: fbr@rice.edu; Fax: (713)285-5154

Annual Report of The Institute of Biosciences and Bioengineering at Rice University - 1995



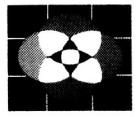
Annual Report of
The Institute of Biosciences and Bioengineering
at Rice University - 1995

Research and Education

Outreach and Special Events

The Institute represents a unique educational environment in which to prepare students to meet the complex scientific, technological, and ethical challenges we face as we head into the twenty-first century.

Message from the Institute Chair



The future of biotechnology-both the discovery of new knowledge and the application of that knowledge to develop new technologies - will increasingly require the combined efforts of experts in many fields. We at Rice University believe it is crucial that future scientists and engineers be exposed to and involved in interdisciplinary activities that teach them to go beyond their chosen fields in pursuit of new knowledge and solutions to problems.

The mission of the Institute is to promote interdisciplinary research and education encompassing the biological, chemical, and engineering disciplines. We pursue this mission by providing opportunities for cross-disciplinary interactions among scientists and engineers at Rice and their colleagues at the nearby Texas Medical Center and at other institutions.

Since its inception in 1986, we have made significant progress toward realizing our vision of the Institute as a center of excellence for innovative cross-disciplinary research and educational programs. The Institute represents a unique educational environment in which to prepare students to meet the complex scientific, technological, and ethical challenges we face as we head into the twenty-first century.

During the past few years we have expanded the original concept of the Institute's mission to include the increasingly important element of outreach - aimed at both the lay public and the academic, medical, and industrial communities of southeastern Texas. Our goal is to establish the Institute as Houston's intellectual center for information-sharing and problem-solving on scientific and technological problems and related issues of public concern.

This past year has been a particularly rewarding one for the Institute and has put us in an excellent position to embark upon a significant phase of growth and development. I am pleased to list here some of our accomplishments during this past 1994-95 academic year, many of which are further highlighted in this annual report:

- Successful application for a NASA Specialized Center of Research and Training (NSCORT) grant in gravitational biology ($5 million over five years)
- Establishment of a new graduate program in bioengineering
- Successful application for a Whitaker Foundation Special Opportunity Award ($750,000 over three years), including two new faculty positions in bioengineering
- Successful preliminary application for a Whitaker Foundation Development Award ($5 million over six years) to establish an undergraduate program in bioengineering, hire six new faculty, and enhance the existing graduate program
- Renewal of the National Institutes of Health Biotechnology Training Grant for an additional five years (1995-2000, $1.5 million over five years)
- Third offering of the "Advances in Tissue Engineering" Short Course in conjunction with the Rice School of Continuing Studies
- Hosting of an FDA Workshop: "Biotechnology Derived Products: Regulatory Policy Issues"
- Successful application for a grant from the Howard Hughes Medical Institute to establish outreach programs for K-12 and women and minority undergraduates to encourage young people in science and to provide opportunities for underrepresented groups
- Publication of "Biotechnology: Science, Engineering and Ethical Challenges for the 21st Century" by the Joseph Henry Press (an arm of the National Academy of Sciences Press) containing the edited proceedings of the second DeLange Conference, hosted by the Institute in the spring of 1994.

Many of the achievements and honors received this past year by individual Institute faculty, students, and staff are also included in this report. We are proud of these achievements and excited about the new challenges and opportunities ahead. With this report, we invite you to share in and continue to support our vision for cross-disciplinary research and outreach and for the education of bioscientists and bioengineers for the twenty-first century.

Larry V. McIntire
E.D. Butcher Professor and Chair
Institute of Biosciences and Bioengineering

Highlights of Cross-Disciplinary Research Collaborations

The Institute has established a network of interdisciplinary and cross-disciplinary research collaborations to increase the knowledge base of Institute faculty, enrich the environment for Institute graduate and undergraduate students, and increase the contacts and resources that support the continued growth of Institute programs.

Cross-disciplinary and interdisciplinary collaborations within the Institute exist among scientists, bioengineers, and faculty from the Texas Medical Center and the Houston biotechnology industry as well as with researchers from other academic and government institutions and biotechnology companies across the country and around the world. This sharing of expertise leads to the development of new research opportunities and provides students the opportunity to expand their research skills and to learn to reach beyond the boundaries of traditional disciplines.

Some of the research collaborations currently under way in the Institute are highlighted on the following pages.

Dr. Frederick B. Rudolph, chair of biochemistry and cell biology and executive director of the Institute of Biosciences and Bioengineering.

Representative Current Collaborations between Institute Faculty and also with the Texas Medical Center and the Houston Biotechnology Industry

Flow Modulation of Cell Adhesion and Metabolism

Larry V. McIntire
Biomedical Engineer,
Rice University

Suzanne Eskin
Texas Biotechnology Corporation,
Houston

C. Wayne Smith
Texas Children's Hospital,
Houston

Garth Nicolson
Tumor Biologist,
M.D. Anderson Cancer Center,
Houston

Three main areas of special interest are currently under investigation: 1. Flow modulation of adhesive interactions of blood borne cells and endothelial cells that line the walls of arteries and veins. Applications include inflammation, arthritis, reperfusion injury, and cancer metastasis; 2. Development of models for thrombosis. The molecular mechanisms of both venous and arterial thrombosis are being investigated, with the goal of developing a new generation of antithrombotic therapeutics; and 3. The role of blood flow and resultant fluid mechanical forces in modulation of intracellular metabolism of vascular cells. Applications include improved understanding of the etiology of atherosclerosis and hyperproliferative diseases of the vascular system as well as targeted gene therapy using endothelial cells or smooth muscle cells as vectors for drug delivery.

Lymphocyte Adhesion

Kyriacos Zygourakis
Chemical Engineer,
Rice University

Larry V. McIntire
Biomedical Engineer,
Rice University

Bradley W. McIntyre
Immunologist,
M.D. Anderson Cancer Center,
Houston

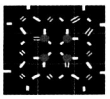
Our team is developing and testing a diagnostic procedure that can directly assay the functional properties of patient lymphocyte populations by monitoring their aggregation rates and analyzing the aggregate morphology. We hope that the lymphocyte adhesion assay will eventually become a standard clinical tool for evaluating patient health and for formulating treatment strategies and analyzing their effectiveness. Through the Technology Transfer Office of the M.D. Anderson Cancer Center, we have already applied to obtain a patent for this assay.

Gene Therapy

Kenneth K. Wu
Professor of Internal Medicine,
UT Health Science Center,
Houston

Antonios G. Mikos
Bioengineer,
Rice University

We have begun investigations using recombinant DNA techniques to evaluate replication-defective retrovirus and adenovirus constructs as vectors for the transfer of human genes. The major technological problems limiting the clinical application of gene therapy include the efficiency of gene transfection into the cells, the efficient transplantation of the transfected cells to the host, the long-term survival of the transplanted cells, the prolonged gene expression, and the controlled (or modulated) release of protein. Solving these problems in a way that minimizes cost to the health care system and maximizes safety will require close collaboration of biomedical engineers, life scientists, and clinical researchers. Rice biomedical engineers and colleagues in the Texas Medical Center are ideally situated to provide leadership in these areas of gene therapy.



Blood Substitutes

J. David Hellums
Chemical Engineer,
Rice University

John S. Olson
Biochemist and Cell Biologist,
Rice University

Guillermo Gutierrez
Professor of Medicine,
UT Health Science Center, Houston

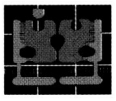
With the increasing worldwide concern about the safety of our blood supply and blood products, there is a great demand for development of blood substitutes. An ongoing interdisciplinary, interinstitutional project involves faculty from biomedical engineering and biochemistry and cell biology from Rice and the University of Texas Health Science Center. The project involves three areas of focus in protein and tissue engineering: blood substitutes and replacement therapies, computational and living engineered model systems, and characterization of tissue structure and function.

Nutritional Immunology

Frederick B. Rudolph
Biochemist and Cell Biologist,
Rice University

Charles T. VanBuren
Transplant Surgeon,
UT Medical School, Houston

With the advent of defined nutritional formulations for infants and for patients in clinical settings, new nutritional requirements are being found. It has previously been assumed that sources of purine and pyrimidines, such as DNA or RNA, were not essential components of the diet. We have discovered a requirement for nucleotides (a source of preformed purine and/or pyrimidine bases) in the diet for maximum cellular immune function. It appears that T-cells are dependent on salvage for nucleotide formation in the G1 phase of the cell cycle and that removal of preformed nucleotides from the diet delays differentiation leading to a decreased cell-mediated immune response. The clinical consequences of this dependence are being evaluated along with basic biochemical studies on the metabolic consequences related to this dietary requirement. A reformulated infant formula and an enteral feeding formulation based on this work are now commercially available.



Cell Transplantation

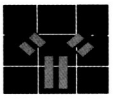
Antonios G. Mikos
Bioengineer,
Rice University

Kenneth K. Wu
Professor of Internal Medicine,
UT Health Science Center,
Houston

Michael J. Yaszemski
Orthopaedic Surgeon,
Wilford Hall Medical Center,
Lackland AFB

Rena Bizios
Biomedical Engineer,
Rensselaer Polytechnic Institute

We are investigating the adhesive interactions between cells and both synthetic and biological substrates to determine the effect of different physical and biochemical factors on cell growth and function. Until recently, most research in the field has focused on minimizing biological fluid and tissue interactions with biomaterials in an effort to prevent fibrous encapsulation from foreign-body reaction or clotting in blood that has contact with artificial devices. In short, much biomaterials research has focused on making the material invisible to the body. Innovations using the inverse approach–programmed extensive interaction of the material with biological tissue–will give biomaterials research a new focus. We are studying bone regeneration and repair using a biodegradable polymer scaffold either by inducing osteoblast growth from the surrounding bone postimplantation or by seeding the scaffold with osteoblasts prior to implantation. We are also exploring a new approach to create hybrid artificial organs by transplanting isolated or encapsulated cell populations into vascularized templates of synthetic polymers.



Arterial Thrombosis

J. David Hellums
Biomedical Engineer,
Rice University

Andrew I. Schafer and
Michael H. Kroll
Baylor College of Medicine,
Houston

Joel L. Moake
Baylor College of Medicine and
Associate Director of the Cox Laboratory
for Biomedical Engineering, Rice University

Our work has shown that flow conditions play an important role in determining platelet reactions. The shear stress field associated with flow in blood vessels can lead to stimulation, functional alterations, and lysis of platelets. Also, it is clear that both the rates and the extent of response of platelets to various agonists depend heavily on the shear field; thus, studies in carefully controlled, known shear fields are particularly significant in elucidating the mechanics and kinetics of platelet reactions. One long-term result of the work will be the development of improved antithrombotic agents.

Arterial Restenosis

Antonios G. Mikos
Bioengineer,
Rice University

Suzanne Eskin
Texas Biotechnology Corporation,
Houston

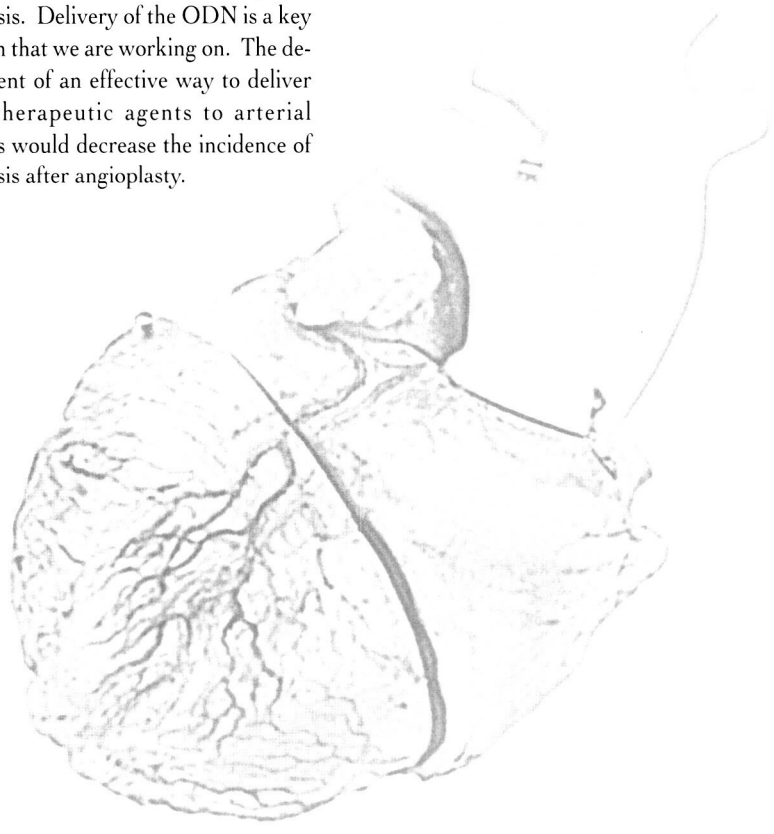
Restenosis of coronary arteries after balloon angioplasty occurs in 25 to 40 percent of clinical cases, generally within two to three months after the procedure. Repeated procedures have a probability of restenosis of up to 70 percent. We are studying antisense oligodeoxynucleotides (ODN), which potentially could provide an effective treatment for restenosis by inhibiting smooth muscle cell proliferation, migration, and matrix synthesis, which contribute to intimal thickening and restenosis. Delivery of the ODN is a key problem that we are working on. The development of an effective way to deliver these therapeutic agents to arterial stenoses would decrease the incidence of restenosis after angioplasty.

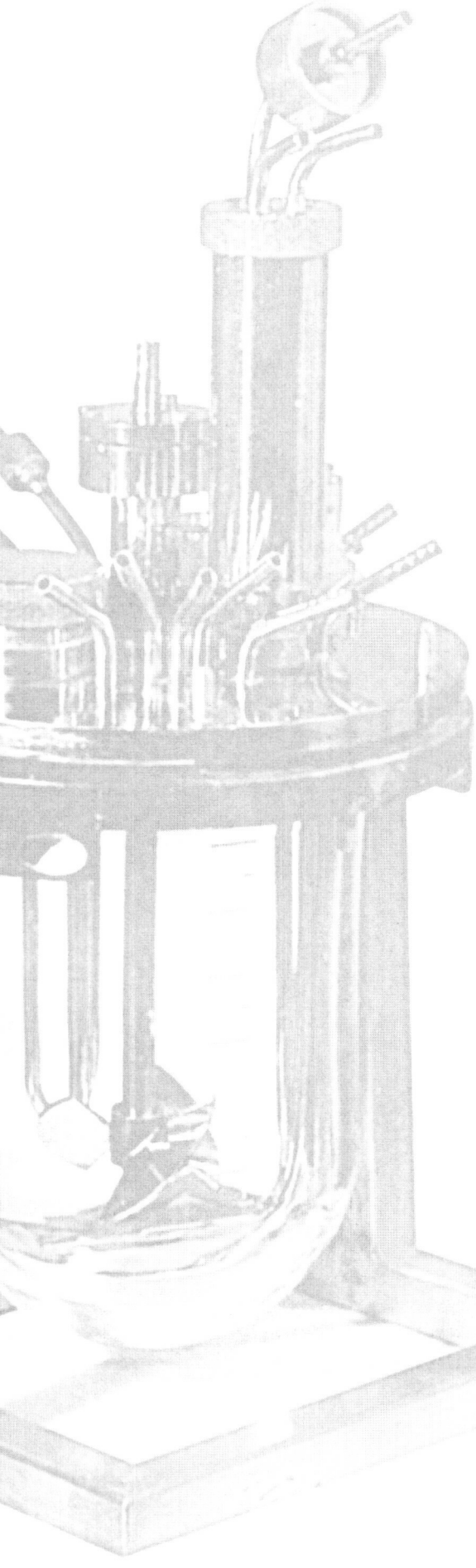
New Protein Expression Systems

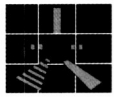
George Bennett
Biochemist and Cell Biologist,
Rice University

Ka-Yiu San
Chemical Engineer,
Rice University

This project involves the use of an acid-induced expression system to produce recombinant proteins in *E. coli.* The project involves both analysis of the mechanism of acid induction and engineering studies to optimize the production levels. In addition, the use of metabolic engineering to reduce limitations on recombinant protein production has provided new avenues to improve production systems.







Bioprocessing

Jacqueline V. Shanks
Chemical Engineer,
Rice University

Michael Gustin
Biochemist and Cell Biologist,
Rice University

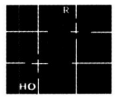
Bioprocesses require knowledge of the metabolism of cells in a reactor environment. NMR spectroscopy can probe the kinetics and physiology of cells in a microreactor in situ. We are collaborating on a project on high osmolarity mutants of the yeast *S. cerevisiae.* Dr. Gustin's lab defined four genes of a new gene family that function to regulate cell growth and gene expression in response to external stimuli. When *S. cerevisiae* is exposed to a medium in which the osmolarity is increased, the yeast increase glycerol synthesis, arresting cell growth until glycerol accumulation is maximal. In situ NMR experiments have provided a powerful, detailed analysis of the metabolic functioning of these genetically altered strains. Osmolarity regulation in yeast exhibits several consequences in carbon utilization and alcohol production and has important applications in the brewing industry.

Fermentation Technology

George Bennett
Biochemist and Cell Biologist,
Rice University

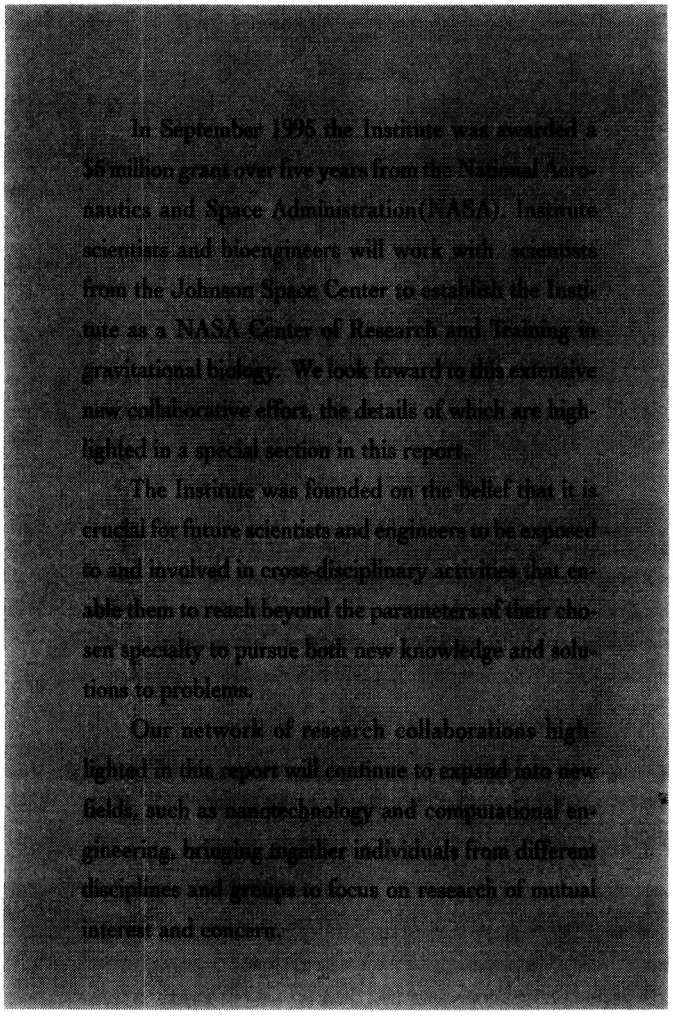
Ka-Yiu San
Chemical Engineer,
Rice University

We are developing a high-level recombinant protein production process in *Escherichia coli* using a pH-inducible promoter system. The use of pH-inducible promoter systems is highly desirable, since reactor pH can be controlled easily and inexpensively by the addition of bulk chemicals. In another project, we are developing a system to release periplasmic proteins from *E. coli* into the fermentation broth without causing significant cell lysis. The capability of releasing product proteins into the broth is highly desirable and will greatly facilitate protein recovery. Work is in progress to adapt this system to a whole cell immobilization system for production of recombinant proteins continuously and extracellularly.



In addition to those highlighted above, twenty other collaborative research projects are also currently being conducted among Institute faculty.

Highlights of Collaborations Among Institute Faculty



In September 1995 the Institute was awarded a $6 million grant over five years from the National Aeronautics and Space Administration(NASA). Institute scientists and bioengineers will work with scientists from the Johnson Space Center to establish the Institute as a NASA Center of Research and Training in gravitational biology. We look foward to this extensive new collaborative effort, the details of which are highlighted in a special section in this report.

The Institute was founded on the belief that it is crucial for future scientists and engineers to be exposed to and involved in cross-disciplinary activities that enable them to reach beyond the parameters of their chosen specialty to pursue both new knowledge and solutions to problems.

Our network of research collaborations highlighted in this report will continue to expand into new fields, such as nanotechnology and computational engineering, bringing together individuals from different disciplines and groups to focus on research of mutual interest and concern.

Selected Collaborations with Industry

- John Olson *(Biochemistry and Cell Biology, Rice University)* and Somatogen, Inc.
- George N. Phillips, Jr. *(Biochemistry and Cell Biology, Rice University)* and Tanox, Inc.
- Antonios G. Mikos *(Chemical Engineering, Rice University)* and Johnson & Johnson
- Jacqueline V. Shanks *(Chemical Engineering, Rice University)* and Proctor & Gamble, Inc.
- Wayne C. Campbell *(Biochemistry and Cell Biology, Rice University)* and Service Corporation International
- Larry V. McIntire *(Chemical Engineering, Rice University)* and Gensia, COR Therapeutics, Centocor, and Texas Biotechnology Corporation
- Frederick B. Rudolph *(Biochemistry and Cell Biology, Rice University)* and Wyeth Ayerst, Inc. and Sandoz Nutrition

Cross-Disciplinary Interactions between Institute Faculty and other Rice University Departments, Institutes, and Centers

Drs. Baruch Brody (Philosophy) and Phil Bedient (Environmental Science and Engineering) served with Institute faculty members Drs. McIntire, Hellums, Rudolph, Matthews, and Schroepfer in 1993-94 on the planning committee for the Second DeLange Conference, which brought together a diverse audience of scientists, engineers, policy leaders, ethicists, and concerned laypersons to discuss the scientific, political, and ethical issues surrounding the current and future directions of biotechnology. Dr. Stanley Reiser (Religious Studies) and Dr. Herb Ward (Energy and Environmental Systems Institute) were also active participants in the Second DeLange Conference.

Collaborations, including possible joint symposia, are being developed with the James A. Baker III Institute for Public Policy.

Institute faculty Drs. Rudolph, Bennett, and Shanks have established ongoing collaborations with Dr. Joseph Hughes (Environmental Science and Engineering).

Highlights of Specialized Areas of Research

Key Areas of Strength and Specialization

The research programs carried out by the Institute faculty can be grouped around the following five key areas of strength and specialization:

- cellular and tissue engineering
- signal transduction
- fermentation, metabolism, and bioprocessing
- sequence, structure, and function
- plant biochemistry and genetics

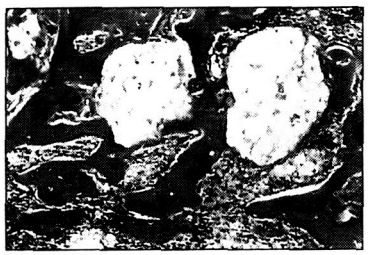
The manner in which these areas of specialization within the Institute are grouped may change over time, reflecting the dynamic nature of the biological sciences.

On the following pages these specialized areas are outlined by the research interests of a few representative faculty working in these areas. The faculty in the Institute may be involved in more than one of these specialized areas of research, as well as other areas of specialization that are being pursued.

Cellular and Tissue Engineering

Faculty: Drs. Hellums, McIntire, Mikos, Moake, Zygourakis, Shanks, San, Clark, Bennett, Rudolph, and Olson

Dr. McIntire's laboratory focuses on understanding the interplay between fluid mechanics, convective mass transport, cell biology, and molecular biology in the cardiovascular system. The experimental approaches fall into three different areas. The first is examination of molecular mechanisms of adhesion for cells that are found in the circulatory system. Specific applications include circulating white blood cells and metastatic cancer cells, both of which must adhere to specific sites in order to migrate through the walls of blood vessels. The second area is the development of models for the formation of thrombotic lesions in blood vessels. Using defined flow conditions, it has been possible to achieve insight into the effects of shear rate and specific compounds on the formation of these lesions in vessels. Finally, the role of blood flow and the consequent forces exerted by fluids on the vascular wall is being examined. In particular, mechanical force modulation of intracellular metabolism of the endothelial cells that line the vessels is being explored, and the transcriptional and translational events that influence cell state and responses are under investigation. Experiments on lymphocyte adhesion are carried out in collaboration with Dr. Zygourakis, whose work focuses on fundamental physical, chemical, and molecular interactions that occur during adhesive processes.



Dr. Hellums's laboratory is examining adhesion and aggregation of human blood platelets and the crucial roles these cells play in hemostatic and thrombotic events in humans. A collaborative research effort with investigators from the Texas Medical Center has shown that flow conditions play an important role in determining platelet reactions. The response of platelets to a variety of stimuli depends heavily on the shear forces to which the cells are subjected. In collaboration with Dr. Olson (biochemistry and cell biology), Dr. Hellums has developed a unique experimental system to determine oxygen fluxes to and from hemoglobin solutions or red cell suspensions under conditions that simulate the microcirculation. To simulate these fluxes, a mathematical model has been developed, and the combination of experimental and theoretical methods is being applied to generate information that will facilitate design of blood substitutes.

Dr. Olson's laboratory applies biochemical, biophysical, and chemical engineering approaches to explore the fundamental processes involved in oxygen transport and storage in mammalian circulatory systems. Using genetically engineered proteins, the dynamics of ligand binding (oxygen, carbon monoxide, etc.) to hemoglobin and myoglobin and their derivatives provide insight into the structural requirements for ligand binding and release. In collaboration with Dr. Phillips, the three-dimensional structures of the myoglobin derivatives are being determined to correlate the actual structural changes with the functional properties of the proteins. The results of these studies are being applied to the design of blood substitutes. Optimization of in vivo and in vitro stability as well as oxygen transport properties (both binding and release) is requisite for a hemoglobin or myoglobin variant that will be a component of blood substitutes. The applications for a substitute for blood that can be used in the field in remote areas in accident, trauma, and military situations are manifold and lifesaving.

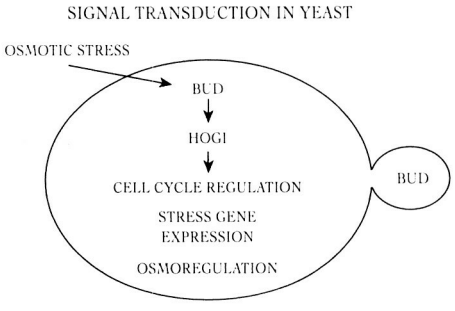
Dr. Mikos's group is studying the reconstruction and repair of tissues by cell transplantation with biodegradable polymers. Using donor material, tissue is dissociated into individual cells, and the cells are attached and grown in a polymeric device. Subsequently, the device is implanted to a site where the cells can function. The polymer is a biodegradable scaffold that organizes the tissue for transplantation. Specifically, liver, cartilage, and bone are being examined.

Dr. Zygourakis is examining the proliferation and migration of anchorage-dependent mammalian cells, since these fundamental processes are essential to wound healing and restoration of endothelial cells in vascular prostheses.

Signal Transduction

Faculty: Drs. Beckingham, de Hostos, Glantz, Gustin, Hellums, Matthews, McIntire, Mikos, Moake, Schroepfer, Stern, and Zygourakis

Dr. Beckingham's laboratory has generated a series of mutants of calmodulin, a protein that plays a major role in regulating cellular events in animal cells. Localized changes in free calcium are employed to regulate metabolism, gene expression, and other processes. These effects are largely mediated by calmodulin, which binds calcium ions and, as a consequence of conformational alteration, binds to and activates a variety of target enzymes and proteins. Both in vitro studies to determine the structure and functional properties of modified calmodulins and in vivo studies to ascertain the effect of mutation on organismal and cellular events are being pursued.



Dr. Gustin's laboratory examines how cells sense and respond to osmotic stress, a project that parallels work in the laboratories of Drs. Braam and McIntire. Genes essential to osmotic responsivity have been cloned, sequenced, and found to be kinases involved in a signalling pathway within the organism. Further studies are under way to determine the nature of these genes' role in the signalling cascade and to identify targets. In addition, Dr. Gustin is examining effects on the actin cytoskeleton during osmotic stress as this network is rapidly disassembled; genes whose products interact with actin to promote reassembly have been identified and are under examination.

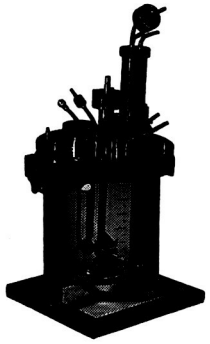
Dr. Glantz and his colleagues examine synaptic mechanisms by which neuronal networks filter, compute, and encode sensory information. The experimental model is the optic lobe of the crayfish, and the emphasis is on neuronal computation of the direction and velocity of moving targets. The participation of specific types of neurotransmitters, their localization in specific neurons, and their action on target cells have been elucidated. Pharmacological manipulation of synapse function has indicated the neurochemistry and mechanisms of selectivity. This information can be employed in generating computational mechanisms of sensory perception.

Dr. Stern's laboratory is involved in analysis of synaptic transmission in *Drosophila*. A combination of genetic, electrophysiological, and molecular methods is being applied to identify and analyze proteins that control synaptic transmission. Genes are identified by mutation, their functions inferred by assaying effects on synaptic transmission, and the genes are cloned and sequenced to enable study at the molecular level.

Fermentation, Metabolism, and Bioprocessing

Faculty: Drs. Bennett, Rudolph, San, Shanks, Campbell, and Stewart

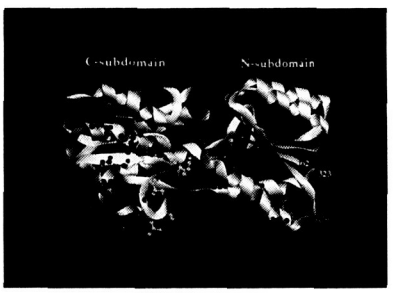
Dr. Rudolph's laboratory examines kinetic, regulatory, and physical properties of enzymes involved in amino acid and nucleotide metabolism. The current proteins on which this laboratory focuses are adenylosuccinate synthetase and adenosine deaminase. Structural and mechanistic analyses are coupled with site-directed mutagenesis and regulatory and developmental analysis of these proteins.



Dr. Campbell's research is directed toward determining the mechanism of translocation of glutamine synthetase into avian liver mitochondria. Most mitochondrial proteins are encoded in the nucleus, translated in the cytosol, and targeted to mitochondria by an N-terminal sequence that is subsequently removed. Glutamine synthetase lacks this presequence, and efforts are under way to identify the amino acids that elicit the translocation to the mitochondria. This targeting process is important to genetic engineering, since proteins must reach the correct destination in transgenic organisms to function properly.

Dr. Bennett's laboratory emphasizes the response of bacteria to the stress of low pH conditions. This area is of particular importance because of the relationship between acidic conditions and the production of toxins or virulence pathogens. Genes that are induced by low pH have been identified, and physiological studies on the mechanism by which low pH affects expression indicate an acid detoxification system. The mechanisms of acid sensing and gene activation are current targets of study.

Dr. San's laboratory focuses on the development of methods for using biological systems as catalysts for production of useful compounds and proteins. Efforts include development of a system to release periplasmic proteins from *E. coli* without causing cell lysis, a capability that facilitates protein recovery and may lead to production of recombinant proteins continuously and extracellularly. In collaboration with Dr. Bennett's laboratory, exploration of a high level pH inducible system for recombinant protein production is under way. In addition, Dr. San's group is examining improved methods for using mammalian tissue cells for protein production.



The laboratories of **Drs. Bennett and Rudolph** are collaborating to explore solvent production in *Clostridia* by metabolic engineering. This project involves purification and characterization of the enzymes involved in acid and solvent production, characterization of the genes and their regulation, and expression of the genes in *Clostridia*. The goal of these efforts is to engineer bacteria that will continuously produce economically important solvents in steady state growth under conditions that have no negative environmental consequences. Dr. San's laboratory will become involved in the later phases of scaling up production processes.

Dr. Stewart's laboratory is examining genetic programming in a model viral system, SPO1 phage of *B. subtilis*. The life cycle of this virus involves at least ten regulatory events in which genes are turned on or off at specific times. Using molecular genetic approaches, mutational analysis of the genes and gene products responsible for each of these events is under study. Information on these regulatory sequences can provide the potential to alter the natural sequence of gene action. In addition, this laboratory is studying the interactions between virus and host that are employed to ensure viral survival. This information will be useful in generating methods to preclude viral reproduction and favor host rather than viral survival.

Sequence, Structure, and Function

Faculty: Drs. Gomer, Matthews, Nikonowicz, Palmer, Parry, Phillips, Price, Clarage, Schroepfer, Walker, and Wilson

Dr. Gomer's laboratory has purified and characterized a protein that is utilized by the slime mold *Dictyostelium discoideum* as a sensing mechanism for the proximity of other cells. This system serves as a model for the mechanisms generally by which cells differentiate and are arranged into organ systems. Cell-cell sensing in terms of spatial orientation and proximity is crucial in these processes. Using molecular biology, genetics, and protein biochemistry, this protein and others that are involved in cell type differentiation and density sensing mechanisms are being identified and characterized.

Dr. Schroepfer's laboratory is involved in understanding the chemistry and biochemistry of cholesterol and other lipids. In particular, this group has examined a number of oxygenated sterols, prepared by chemical synthesis, which have been found to be very potent inhibitors of cholesterol biosynthesis. Interrelationships in the biosynthesis, metabolism, and regulatory effects in cell function of cholesterol and sphingolipids and their metabolites are emphasized.

Dr. Matthews's laboratory is examining the structure and function of DNA binding proteins that are involved in regulating gene expression in both prokaryotic and eukaryotic organisms. Using genetically engineered derivatives and a wide range of chemical and physical methods, the contributions of specific domains and selected amino acid residues to the functional properties of the lactose repressor protein are being explored. Ultrabithorax, a homeodomain-containing protein essential for segmentation in *Drosophila*, is also under study, employing unique DNA constructs with variable numbers and spacing of target sequences.

Dr. Palmer's laboratory focuses on the proteins that catalyze electron transfer reactions in the mitochondria; these enzymes are the mechanisms by which energy that originates in the diet is made available to the cell. Two of these proteins, ubiquinol cytochrome c oxidoreductase and cytochrome oxidase, are the primary targets of study. The methods employed are primarily spectroscopic and kinetic to determine transient states of these enzymes

and to construct the electron and proton translocation reactions.

Dr. Phillips's laboratory examines three-dimensional structure and dynamics of biomolecules and relates these properties to function. Emphasis is on the molecular mechanisms involved in the regulation of muscle contraction. The specific proteins involved in the regulatory process under study are tropomyosin, actin, and troponin. In addition to application of x-ray crystallographic techniques to the study of this important system, theoretical analysis and development of other diffraction methods provide additional insights into the modes of actions of these proteins.

The goal of **Dr. Nikonowicz's** laboratory is to obtain a better understanding of the structure-function relationships underlying biologically relevant nucleic acid systems using heteronuclear nuclear magnetic resonance spectroscopy and a variety of computational methods.

Plant Biochemistry and Genetics

Faculty: Drs. Braam, Gibson, Shanks, and Bartel

Dr. Braam's research group is identifying the genes and proteins that are involved in mechanosensory pathways in plants and determining the ways in which mechanical stimulation alters developmental pathways. This emphasis on mechanical stimulation in some ways parallels the studies of Dr. McIntire's laboratory on the effects of shear stress on endothelial cells. Interestingly, three of the five gene sequences identified as mechanically responsive in plants appear to be calcium binding proteins, including calmodulin. This result suggests that calcium may play as important a role in plant cells as in animal cells.

Dr. Shanks's laboratory is exploring the use of "hairy root" cultures of periwinkle for production of pharmaceutically active compounds. These clones grow rapidly and carry out the secondary metabolite pathways necessary for generation of most active compounds. These methods apply not only to production of anticancer compounds from periwinkle but also to other plant products that are biologically active (e.g., taxol, trichosanthin).

Dr. Gibson's research interests are the regulation of membrane composition and role of membrane composition in determining cellular properties and source-sink interactions in plants.

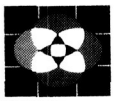
Dr. Bartel's research interests are concerned with the genetics of auxin regulation in *Arabidopsis* development, with the expectation that major features of auxin regulation deciphered there will be general to the plant kingdom. Manipulating these regulators will allow modulation of auxin levels to influence development and uncover the many roles of auxin in the plant life cycle. The ability to control auxin levels also has applications in agriculture, in which control of plant size and shape is crucial.

We are extremely pleased to have very recently added two faculty in the plant biochemistry and genetics area (Drs. Gibson and Bartel both recently joined the biochemistry and cell biology department). Adding the strengths of these new faculty to those of Dr. Braam (biochemistry and cell biology) and Dr. Shanks (chemical engineering), we have a very strong group from which to build a dynamic program in this emerging new field.

As with many of the emerging new specialty areas within the biosciences and bioengineering, it is very possible to attain national ranking with a small number of faculty. We believe we can build our specialized research areas into programs of national ranking because of the high quality of the faculty we now have and because of the Institute's strength in outreach and cross-disciplinary interactions, which makes great use of a large network of intellectual resources from the academic, medical, and industrial communities within and outside of the Institute and the university.

As an example, a recent study conducted by the National Research Council, an independent organization chartered by Congress entitled "Research Doctorate Programs in the United States" ranked Rice tenth in scholarly quality and fourth in teaching effectiveness in the field of biomedical engineering.

Recent Activities and Achievements of Institute Faculty



Dr. Kathleen M. Beckingham

- Texas Advanced Technology Program (ATP) grant (with Dr. Michael Stern). The in vivo role of calmodulin in neural function
- Robert A. Welch Foundation Grant renewed
- Best Presentation Award, FASEB Conference on Calcium and Cell Function, July 1994
- Invited speaker, Ninth International Symposium on Calcium Binding Proteins, May 1995
- NASA grant, Role of Gravity in Early Embryonic Pattern Formation

Dr. George Bennett

- Invited speaker at American Society of Microbiology and the Society for Industrial Microbiology on metabolic engineering
- Robert A. Welch Foundation grant to develop methods for manipulating and assembling large DNA fragments
- Renewal of collaborative Department of Energy (DOE) and U.S. Department of Agriculture (USDA) grants (with Dr. Frederick B. Rudolph) to study events related to solvent production in *Clostridia*
- NSF grant (with Dr. Ka-Yiu San) to analyze and manipulate metabolic fluxes in bacteria
- EPA/HSRC collaborative grant with Dr. Frederick B. Rudolph and Dr. J. B. Hughes (environmental engineering) to study biodegradation of TNT by *Clostridia*
- NASA grant (with Dr. Frederick B. Rudolph), Microgravity: Effects on Microbe-Host Interactions

Dr. Janet Braam

- NIH First Award, Signal transduction and gene regulation in *Arabidopsis*
- New five-year NSF grant to study regulation and function of genes encoding cell wall modifying enzymes
- NASA grant, Calmodulin-related proteins in mechanostimulated plants
- Invited speaker at eight universities, conferences, or seminar series during 1994-95
- Member of NASA and NSF study sections
- Invited participant at the White House Forum on Health, Safety and Food for America sponsored by the Office of Science and Technology
- NASA grant, Molecular and Developmental Responses of Plants to Mechanical Stimuli

Dr. J. Wayne Campbell

- Member, Review Committee for LEQSF proposals in biological and medical sciences, Baton Rouge, Louisiana, 1994

Dr. James Clarage

- NSF grant to study structure and dynamics of macromolecules using x-ray diffraction
- Invited speaker, Biophysical Society, San Fransisco, California, 1995
- Essay published in the international magazine, *WIRED*

Dr. John W. Clark, Jr.

- Named founding fellow of the American Institute of Medical and Biological Engineering

Dr. Susan I. Gibson

- New DOE grant, A molecular-genetic approach to studying source-sink interactions in *Arabidopsis*

Dr. Raymon M. Glantz

- Renewal of NSF grant, Synaptic mechanisms of directionally selective movement detection

Dr. Richard Gomer

- New March of Dimes grant, Cell density sensing in *Dictyostelium*
- New Robert A. Welch Foundation grant, Regulation of cAMP synthesis
- Renewal of Howard Hughes Medical Institute appointment

Dr. Michael C. Gustin

- New American Cancer Society grant, Osmosensing signal transduction pathways
- Renewal of NSF grant (five years), Signal mediated growth control by osmotic stress
- NASA grant, Pressure-sensing MAP Kinase Cascades in Yeast and Mammals

Dr. J. David Hellums

- NIH MERIT Research Award for the period 1986-1996
- Biomedical Engineering Society Award: Whitaker Foundation Distinguished Lectureship
- Elected a founding member of the American Institute of Medical and Biological Engineering
- Elected to senior membership in the Biomedical Engineering Society
- Elected to the Board of Directors of the Biomedical Engineering Society
- Special Professorship in Biomedical Engineering, University of Tsukuba, Japan, Spring Semester, 1995
- Lecturer at the University of Tsukuba and at seven other universities and research institutes in Japan

Institute faculty research has received major support from national and regional foundations, both government and private.

Dr. Kathleen S. Matthews

- Nominating committee, ASBMB
- Review Committee, Howard Hughes Medical Institute
- Associate Editor, Journal of Biological Chemistry
- Funding from the Dunn Foundation for "High Performance Computing Research in Computational Biology"
- Funding from the Markey Foundation for "Research Instrumentation for Biosciences"

Dr. Larry V. McIntire

- President, Biomedical Engineering Society, 1995-96
- President, North American Society for Biorheology, 1994-97
- Elected Secretary-Treasurer of the American Institute for Medical and Biological Engineering, 1995-97
- Named a Fellow of the American Institute of Chemical Engineers, 1995
- Principal Investigator: Whitaker Foundation Special Opportunity Award, 1995-97
- Principal Investigator: NASA-National Specialized Center of Research and Training in Gravitational Biology, 1996-2001
- Renewal of NIH MERIT Award, 1995-2000
- Executive Committee, Council on Thrombosis, American Heart Association, 1995-97
- Sigma Xi National Lecturer, 1993-95
- Executive Committee, U. S. National Committee on Biomechanics, 1994-96

Dr. Antonios G. Mikos

- 1994 Whitaker Young Investigator Award, Biomedical Engineering Society
- 1995 Hershel M. Rich Invention Award, Rice University
- Research Advisor of Best Undergraduate Polymer Research, POLYED Award, American Chemical Society, 1995
- Research Advisor of Best Poster, Intermedics Award, Houston Society for Engineering in Medicine and Biology, 1995
- Invited Lecturer, American Association for the Advancement of Science Meeting, Atlanta, Georgia, 1995
- Keynote Lecturer, First International Congress on Cellular Therapy & Tissue Engineering, Washington, D.C., 1995
- Editor, *Tissue Engineering*, 1995
- Organizer of Third Annual Continuing Education Course, "Advances in Tissue Engineering," 1995
- Whitaker Foundation Grant, Polymeric Delivery Systems for Antisense Oligonucleotides
- NASA grant, Mechanical Load Effects on Bone Formation

Dr. Joel Moake

- NIH grant, Molecular mechanisms of platelet thrombosis under flow (four years)

Dr. Edward P. Nikonowicz

- NIH grant, NMR studies of RNAs and RNA protein interactions
- Welch grant, Development of Heteronuclear NMR methods to probe RNA structural motifs

Dr. John S. Olson

- Invited lecturer at Kyoto University, Osaka University, and Institute for Molecular Design, Okazaki, Japan, March, 1995
- Member of NIH Cellular and Molecular Biophysics (BBCA) Study Section
- Scientific consultant to Somatogen, Inc.
- Continuing NIH grants, Functional properties of hemoglobins and myoglobins and the design of heme-protein based blood substitutes
- Welch Foundation grant, Stereochemical mechanisms of ligand binding to heme proteins
- New Texas Advanced Technology Program (ATP) grant (with Dr. George Phillips), Synthetic Heme Cofactors In Engineered Globins as Physiological Ligand Biosensors

Dr. Graham Palmer

- Invited lecturer, Second IUBMB Congress on Molecular Biology, Bari, Italy
- MERIT renewal of NIH grant, Molecular mechanism in biological redox-reactions
- Renewal of Welch Foundation grant, Electron transfer reactions

Dr. Ronald J. Parry

- Grant renewal from National Institute of General Medical Science (NIGMS) (four years), Biosynthesis of some microbial metabolites
- Associate Editor, Natural Product Letters
- Invited lecturer, Gordon Conference on Purines and Pyrimidines, July 1995

Dr. George N. Phillips, Jr.

- Grant renewal from NIAMS (five years), Structural determinates of ligand binding to myoglobin
- Invited lecturer, Gordon Conference on x-ray physics, August 1995
- Renewal of Welch Foundation grant, Protein Dynamics
- New Texas Advanced Technology Program (ATP) grant (with Dr. John Olson), Synthetic Heme Cofactors In Engineered Globins as Physiological Ligand Biosensors

Dr. Maureen G. Price

- Muscular Dystrophy Association basic research grant renewal (three years), Skelemin: mammalian muscle cytoskeletal/M-disc protein
- John F. Smiekel Foundation Research Grant, (four years), Muscle structural proteins antecedent to the immunoglobulin superfamily
- Codirector, Rice Undergraduate Scholars Program (Honors 470-471), 1993-1996
- Invited lecturer, American College of Sports Medicine, May 1996

Faculty members are frequently recognized by national professional societies as members, officers, and invited conference lecturers.

- Coorganizer of Houston Motility and Cytoskeleton Group (with Dr. Amy McGough, Baylor College of Medicine, 1995-)

Dr. Frederick B. Rudolph

- Howard Hughes Medical Institute Undergraduate Biological Science Initiative Grant
- Grant from Hoblitzelle Foundation for joint program with high schools in Rio Grande Valley
- NIH Biotechnology Training Grant renewal, 1995-2000
- Patent under review
- Faculty member, Project Kaleidoscope Meeting on Biological Sciences Curriculum, University of Oregon, May 1995
- Panel Member, HHMI Program Directors Meeting, October 1995
- Coprincipal Investigator: NASA-National Specialized Center of Research and Training in Gravitational Biology, 1996-2001

Dr. Ka-Yiu San

- NSF grant (with Dr. George Bennett) to analyze and manipulate metabolic fluxes in bacteria
- Coinvestigator (with Dr. Jacqueline Shanks), NSF grant entitled "HPLC Photodiode Array and System Upgrade"

Dr. George J. Schroepfer, Jr.

- 1992-95: twenty-six publications, ten patents awarded, six additional patents currently under review
- Invited lecturer at the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences
- Lecturer at the University of Tokyo, Sapporo University College of Medicine, the National Cardiovascular Research Center of Japan, Niigata University School of Medicine, and Showa University School of Pharmaceutical Sciences, University of Texas Medical School at Houston, University of Texas Medical School at Galveston, Baylor College of Medicine, University of California at Los Angeles
- Scientific research collaborations with scientists at a number of institutions, including: The Jackson Laboratory (Bar Harbor, Maine), the Salk Institute, Southwestern Medical School, Baylor College of Medicine, University of Pennsylvania School of Medicine, University of California at Los Angeles School of Medicine, University of Texas Medical School at Houston, Johns Hopkins School of Medicine, Upjohn Company, University of Niigata School of Medicine (Niigata, Japan), National Institutes of Health of Japan (Tokyo), and Pasteur Institute (Lille, France)
- New grant from National Institutes of Health, "Sphingolipids and Sterols: Metabolism and Interactions"
- New grant from Texas Advanced Technology Program, "Development of New Oxysterols for Potential Use in Medicine"
- New grant from March of Dimes Birth Defects Foundation, "Role of Defects in Sterol Biosynthesis in the Pathogenesis of Congenital Developmental Diseases"
- Renewal grant fromRobert A. Welch Foundation, "Synthesis, Structure, and Spectral Properties of Natural Products"
- Guest Associate Editor, Journal of Lipid Research, 1994, 1995
- Member of Editorial Board, Current *Pharmaceutical Design*, 1995

Dr. Jacqueline V. Shanks

- 1992-1997 NSF National Young Investigator Award, "In situ NMR spectroscopy of metabolically engineered plant and yeast cultures"
- Professional Progress in Engineering Award, Iowa State University, 1994
- New NSF grant (with Dr. Ka-Yiu San) entitled "HPLC Photodiode Array and System Upgrade"
- New EPA grant (with Dr. Joseph Hughes) entitled "In situ Biochemical Remediation of Trinitrotoluene Contaminated Soils"
- NRC Committee Member on Biobased Industrial Products, 1994-1995
- American Chemical Society Alternate Councilor, BIOT Division, 1995-1998
- New Texas Advanced Technology Program (ATP) grant, Phytoremediation of TNT

Dr. Michael Stern

- New grant from NIGMS (five years), Control of synaptic transmission in *Drosophila*
- New grant from Texas ATP (with Dr. Kathleen Beckingham), "The in vivo role of calmodulin in neural function"
- New grant from American Heart Association (three years), "Cloning of P669, a gene affecting neuronal excitability in *Drosophila*"
- NASA grant, Role of Gravity in the Development and Function of the *Drosophila* Nervous System

Dr. James B. Walker

- Publication in J. Bacteriology, February 1995-Biosynthesis of spectinomycin-antiobiotic.
- Invited symposium lecturer on bioenergetic engineering, Antwerp, Belgium

Dr. Kyriacos Zygourakis

- New NSF grant (with Dr. Larry V. McIntire), 1995-1998, to study the migration and proliferation of endothelial cells
- Patent awarded on lymphocyte adhesion assay
- NASA grant, "Microgravity Effects on Lymphocyte Adhesion and Motility"

New Faculty Members

Association with the Institute and the new facilities at George R. Brown Hall have enabled departments to recruit outstanding new faculty.

This year the Institute welcomes three new faculty members. Drs. Bonnie Bartel and Eugenio de Hostos have joined the Department of Biochemistry and Cell Biology, and Dr. Seiichi Matsuda has accepted a joint appointment with the Department of Chemistry and the Department of Biochemistry and Cell Biology.

Bonnie Bartel

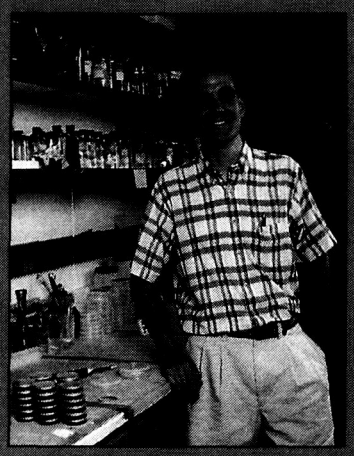
Assistant Professor

Bonnie Bartel

B.A., Bethel College, KS, 1985 (Biology) • Ph.D. Massachusetts Institute of Technology, 1990 (Biology) • American Cancer Society and NSF Postdoctoral Fellow, Whitehead Institute for Biomedical Research, 1991-1995 • Faculty member, Rice University, 1995-present

The major focus of research in our laboratory is deciphering the molecular mechanisms by which levels of the plant hormone auxin are regulated. Auxins are plant signaling molecules that are involved in both developmental events, such as embryo symmetry establishment and root initiation, and environmental responses, including gravitropism and phototropism. Whether a plant cell develops as a root or a shoot is in part determined by the local concentration of auxins. Although the gross effects of altering auxin concentrations were first observed decades ago, how these phenomena occur at a molecular level remains so obscure that not even the auxin biosynthetic pathway has yet been determined in plants. The enzymes that inactivate auxins are only beginning to be described, and the signal transduction pathways by which auxins exert their effects have not been elucidated.

We are exploring the molecular bases of auxin regulation and the roles of auxin in growth and development using the flowering plant *Arabidopsis thaliana*. Levels of the predominant auxin, indole-3-acetic acid (IAA), can be controlled in plants by altering rates of synthesis and degradation as well as by conjugation to and deconjugation from amino acids or carbohydrates. We have isolated *Arabidopsis* mutants with defects in IAA deconjugation and have cloned one of the genes defective in these mutants using positional information. We are also studying the role of indole-3-acetonitrile (IAN) hydrolyzing enzymes in IAA biosynthesis. We are ectopically expressing IAA metabolic genes in transgenic plants to modulate IAA levels in vivo and elucidate the many roles of auxin in the plant life cycle. Using a combination of classical genetic analyses in plants and functional screens in yeast, we are isolating additional mutants and genes involved in auxin biosynthesis, conjugation, deconjugation, and degradation in order to unravel the complex mechanisms by which auxin levels are controlled. By identifying both upstream and downstream regulators of IAA, ultimately we will be able to modulate IAA levels in the plant and observe the consequences at the organismal, tissue, and cellular levels.



Eugenio L. de Hostos

B.S., Yale University, 1983 • Ph.D., Stanford University, 1989 • Postdoctoral Fellow, Planck Institute for Biochemistry, Martinsried, Germany, 1989-1992 • Postdoctoral Fellow, University of California, San Francisco, 1992-1995 • Faculty member, Rice University, 1996-present

Eugenio L. de Hostos

Assistant Professor

Moving themselves around and moving things inside of them are two of the fundamental processes of eukaryotic cells. The intricately regulated and complex machinery behind these processes is the cytoskeleton, which has two major divisions: the actin-based microfilament system and the tubulin-based microtubule system.

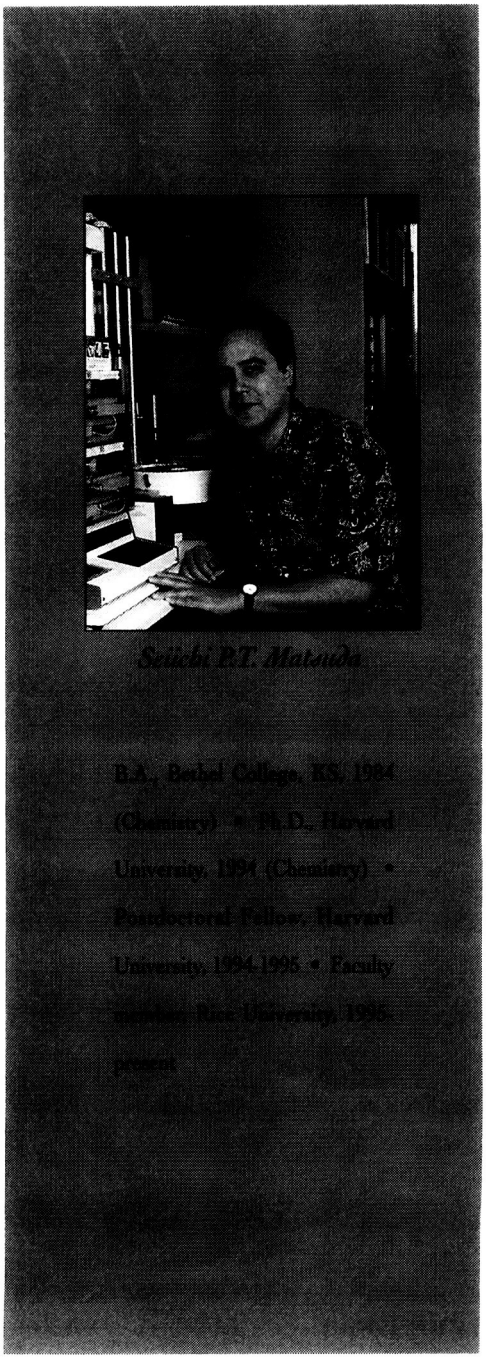
My laboratory is engaged in projects aimed at identifying and analyzing components of both systems using the tools of biochemistry, molecular biology, and microscopy. As an experimental system we use the cellular slime mold *Dictyostelium discoideum*, which resembles in many ways the ameboid cells of higher eukaryotes. Much work has shown that the ability of most cells to migrate depends largely on actin (in filamentous or monomeric form) and on proteins that interact with this molecule. It is thought that actin-binding proteins are the targets of signal transduction pathways that make cells such as a macrophage or *Dictyostelium* respond to a chemotactic signal. Our work in the area of the actin cytoskeleton focuses on actin-binding proteins. We are currently analyzing mutants generated by gene disruption that lack a particular actin-binding protein and are defective in cell locomotion and cell division. Molecular motors that move along microtubule tracks are involved in transporting organelles, including chromosomes and secretory vesicles within eukaryotic cells. Based on their peptide sequence the motors can be grouped into two families, the dyneins and the diverse family of kinesin-like proteins (klps). We have identified six klps in *Dictyostelium* and are in the process of assigning specific roles to individual proteins biochemically by using in vitro motility assays and by generating mutants by gene disruption.

Seiichi P.T. Matsuda

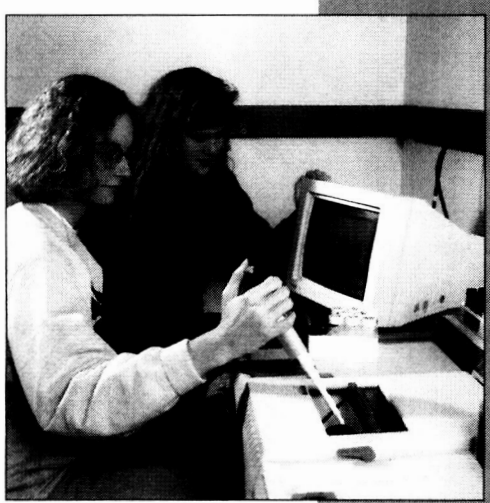
Assistant Professor

Terpenoids are compounds derived from isopentenyl pyrophosphate. They are the most numerous and structurally diverse group of natural products, with 22,000 members displaying more than three hundred ring systems. Terpenoids that play crucial roles in vertebrates include the retinoids; the geranyl and farnesyl protein anchors; the coenzymes Q, vitamins A, D, and E; cholesterol; and the steroid hormones. Terpenoid hormones and pheromones appear to be equally important in invertebrates. In plants, the gibberellins, the brassinosteroids, and abscisic acid are terpenoid regulatory molecules. Many plants synthesize defense terpenoids that would interfere with biological processes in potential herbivores. Some of these compounds are medicinally useful, such as taxol (anticancer), compactin (hypocholesterolemic), and digitoxin (cardiotonic). Finally, terpenoids are important components of flavor and fragrance. Example terpenoid flavors are glycyrrhetic acid (licorice), carvone (spearmint), limonene (lemon), and pinene (gin). Terpenoids account for the distinctive flavor of nearly every herb and are the scent components of rose, musk, sandalwood, patchouli, and cedar, among myriad others.

We investigate terpenoid biosynthesis, primarily using molecular biological techniques to study the major classes of enzymes that contribute to terpenoid diversity: oligoprenyl pyrophosphate synthases, terpene synthases, and terpene oxidases. Terpene synthases catalyze spectacular reactions, such as the conversion of epoxysqualene to cycloartenol. The genes that encode these enzymes are keys that permit access to many arenas of terpenoid biochemistry. We have learned surprisingly much about the roles that specific amino acid residues play in catalysis simply by thoroughly analyzing sequence data. We are using this structural information to design and synthesize drugs that disrupt the biosynthesis of essential terpenoids in pathogenic organisms. We are reconstructing terpenoid biosynthetic pathways to develop microorganisms that produce valuable compounds, many of which are difficult to synthesize or extract from natural sources. We will manipulate biosynthesis of regulatory terpenoids in the plant *Arabidopsis thaliana* to investigate the biological functions of these molecules.



Graduate Programs and Curriculum Development



In the future, molecular biologists will have to learn a variety of engineering techniques. Similarly, the next generation of bioengineers will have to acquire fundamental knowledge of biology and biochemistry. The recent National Research Council report, "Putting Biotechnology to Work: Bioprocess Engineering," emphasizes the need for this new kind of engineering if the United States is to capture the fruits of its investment in molecular and cell biology.

The graduate programs of the Institute of Biosciences and Bioengineering at Rice directly and effectively address this need for a more comprehensive curriculum incorporating both biology and engineering.

Graduate study leading to the Ph.D. in biology, biochemistry and cell biology, chemistry, chemical engineering, and electrical and computer engineering is offered. Students are formally affiliated with a department and carry out research in one of the three major laboratories of the Institute. This year the Institute introduced a new graduate program leading to a Ph.D. in bioengineering. The curriculum will be based on newly discovered fundamental knowledge, combining molecular and cell biology advances with a quantitative systems approach. The graduate curriculum includes a core of required courses to give the basic science and engineering background we believe will be required for the twenty-first century bioengineer. The new program is highlighted in more detail below.

Having highly trained, creative bioengineers will contribute to U.S. industrial competitiveness and will be crucial for translating our world leadership in the scientific aspects of biotechnology into cost-effective industrial and product applications. We strongly believe that the new bioengineering curriculum will have a major national impact on the evolving paradigms of bioengineering and will prepare our students to be leaders in translating science to biotechnology applications for the year 2000 and beyond.

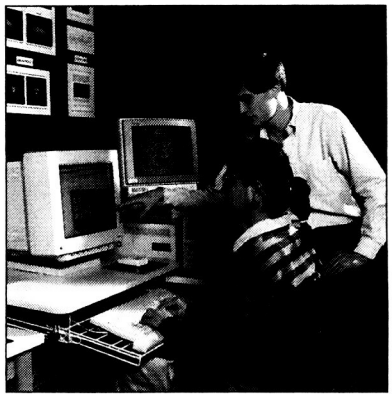
Having highly trained, creative bioengineers will contribute to U.S. industrial competitiveness and will be crucial for translating our world leadership in the scientific aspects of biotechnology into cost-effective industrial and product applications.

Interdisciplinary Bioengineering Programs

Bioengineers will need interdisciplinary skills in the biological sciences, modern materials science, computer science, and systems modeling. This year we introduced a new graduate program leading to a Ph.D. in bioengineering that will prepare our students to interact directly with cell and molecular biologists but still retain the quantitative modeling capability so important for real engineering applications.

The graduate curriculum allows for three specific areas of focus within bioengineering: cellular and molecular engineering, biomechanics and biomaterials, and systems engineering and instrumentation. To implement the new curriculum, six new and two completely modified bioengineering courses are being developed, targeted at first-year graduate students. Elective courses in each of the three areas of focus complement the core requirements and allow concentration in a specific aspect of the broad field of bioengineering.

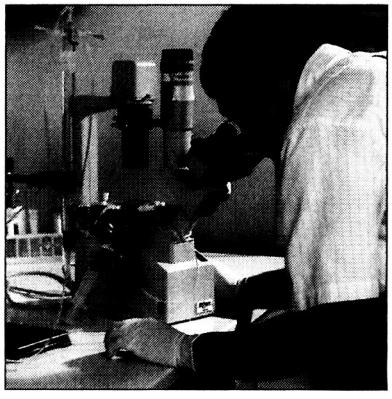
A recent study of research-doctorate programs by the National Research Council ranked the biomedical engineering graduate program at Rice University tenth in scholarly quality and fourth in teaching effectiveness.



Biotechnology Training Program

Funded by a grant from the National Institutes of Health, the program provides stipends and research support in a variety of disciplines for graduate students interested in a research career in biotechnology. The program allows students access to the tools of biotechnology while specializing in a particular research area. Students receive training in broad areas of biotechnology that relate to commercial application of these techniques.

A core of interdisciplinary courses is offered and includes a three- to six-month internship in an industrial setting. Students from the Departments of Biochemistry and Cell Biology, Chemistry, Chemical Engineering, Electrical and Computer Engineering, and others participate in the program.

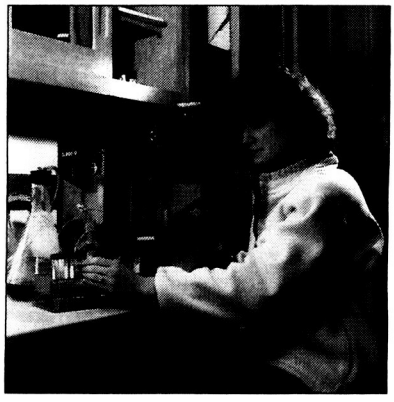


Other Training Programs

Support for graduate training is also provided by another National Institutes of Health grant (in molecular biophysics) and by a recently awarded grant from the National Aeronautics and Space Administration. This new program is highlighted in a special section in this report.

Opportunities for studies in computational aspects of modern biology and biochemistry are available through the Keck Center for Computational Biology, a joint effort of Rice University, Baylor College of Medicine, and the University of Houston. Fellowship support is available for students willing to take courses in both computational science and the biosciences.

Joint M.D./Ph.D. Programs are available in various laboratories of the Institute in conjunction with Baylor College of Medicine and the University of Texas Health Science Center at Houston.



Ph.D. Graduates

The quality of faculty research and expertise, coupled with world-class physical facilities, attracts highly qualified graduate students to Rice who go on to pursue careers in biotechnology, engineering, and medicine.

Since the Institute's inception in 1986, 130 students have received Ph.D.s from the member departments of the Institute of Biosciences and Bioengineering.

We are proud to list them here and to report on their progress since graduation.

Biochemistry and Cell Biology Department

1986

Bruce F. Cooper, Lecturer and Coordinator of Laboratory Training, Department of Biochemistry and Cell Biology, Rice University

Thomas J. Daly, Staff Scientist, Repligen, Cambridge, Mass.

Akihiro Izumi, Anesthesiologist, St. Joseph's Hospital, Houston

Robert J. Kauten, Research Associate, Department of Food Science and Technology, University of California, Davis

Russell E. McKinnie, Research Scientist, Monsanto, St. Louis, Mo.

Sharon (Yoder) Roth, Assistant Professor, Department of Biochemistry and Molecular Biology, M.D. Anderson Cancer Center, Houston

Alice Rubacha, At home with three small children, San Francisco, Calif.

David M. Turner, Assistant Director of Research Planning, Department of Drug Safety and Metabolism, Sandoz Pharmaceutical Company, East Hanover, N.J.

Peggy A. Whitson, Deputy Director of Life Sciences, Biomedical Operations and Research Branch, NASA, Houston

1987

Artemis E. Chakerian, Research Scientist, University of New Mexico, Albuquerque

1988

Elizabeth A. Auger, Assistant Professor, Department of Therapeutic Radiology, University of Minnesota Health Center, Minn.

William C. Fanslow, Research Scientist, Immunex Corporation, Seattle, Wash.

W. Richard Light, Research Scientist, Biopure, Inc., Boston, Mass.

David W. Myers, Research Scientist, Walt Disney Memorial Cancer Center, Orlando, Fla.

Thomas N. Pajewski, Assistant Professor, Department of Anesthesiology, University of Virginia Medical School, Charlottesville

Nadine Ritter, Research Scientist, Abbott Laboratories, Abbott Park, Ill.

Ann O. Sperry, Postdoctoral Associate, University of Texas Southwestern Medical School, Dallas

John C. Spurlino, Research Investigator, Sterling Winthrop Pharmaceuticals Research Division, Collegeville, Pa.

Mark A. Tucker, Research Associate Professor, University of Southern California School of Dentistry, Los Angeles, Calif.

Polly S. Vermersch, Associate, Howard Hughes Institute of Structural Biology, Baylor College of Medicine, Houston

Martin X. Zillman, Research Scientist, private company, New York

1989

Wei-Yuan Chou, Assistant Professor, National Defense University, Taiwan

Douglas D. Lemon, Research Scientist, Somatogen, Inc., Boulder, Colo.

Ronald J. Roblfs, Research Assistant Professor, Department of Medicine, University of California, San Diego

Scott D. Rose, Postdoctoral Associate, Southwestern Medical School, Dallas

1990

Tamsen V. de Valoir, Attorney, Houston

Kevin E. Doyle, Research Scientist, biotechnology company, Boston, Mass.

Joseph A. Gardner, Instructor and Editor, Japanese Chemical Society, Narita, Japan

Bruce L. Jacobsen, Research Associate, Enzyme Institute, University of Wisconsin, Madison

Hartmut Luecke, Postdoctoral Fellow, Linear Accelerator Center, Stanford University, Stanford, Calif.

Dolores H. Needleman, Instructor, Baylor College of Medicine, Houston

Cindy Pfeiffer-Linn, Assistant Professor, Louisiana State University Medical School, New Orleans, La.

Richard W. Welch, Postdoctoral Fellow, National Institutes of Health, Bethesda, Md.

Kyle L. Wick, Postdoctoral Fellow, Emory University, Atlanta, Ga.

1991

Susan Chacko, Postdoctoral Associate, National Institutes of Health, Bethesda, Md.

John F. Maune, Overseas studies, Sapporo, Japan

Daniel J. Petersen, Postdoctoral Research Fellow, University of British Columbia, Vancouver, Canada

1992

Rui Brito, Assistant Professor, Universidade de Coimbra, Portugal

Jack Howarth, Site Manager, Structured NMR Facility, University of Cincinnati, Ohio

Yuan-Ching Liu, Postdoctoral Associate, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, Conn.

Shi-Yuan Meng, Research Scientist, Amgen, Inc., Thousand Oaks, Calif.

Lynne E. Rodseth, Postdoctoral Fellow, Department of Structural Biology, University of Texas Southwestern Medical Center, Dallas

Ita Yuen, Research Associate, DuPont, Wilmington, Del.

1993

Robert E. Brantley, Jr., High School Science Teacher, Dublin, Ga.

T.E. Carver, Postdoctoral Fellow, Department of Biochemistry, Penn State University, Pa.

Jie Chen, Postdoctoral Fellow, Department of Chemistry, Harvard University, Cambridge, Mass.

Kathleen M. Gajewski, Postdoctoral Fellow, M.D. Anderson Cancer Center, Houston

K.A. Johnson, Postdoctoral Fellow, Howard Hughes Institute of Structural Biology, Baylor College of Medicine, Houston

Purnima R. Laud, Postdoctoral Fellow, Department of Immunology, M. D. Anderson Cancer Center, Houston

1994

Jay L. Brewster, Postdoctoral Fellow, McLaughlin Researchers, Great Falls, Montana

Wen-I Chang, Research Scientist, Tanox Inc., Houston

Sumita Chowdhury, Postdoctoral Fellow, Department of Radiology, University of California at San Francisco

Renu Jain, Research Associate, Baylor College of Medicine, Houston

KeYin Tu, Private company, San Antonio

Ping Wei, Postdoctoral Fellow, Salk Institute, La Jolla, Calif.

1995

Anand R. Kolatkar, Postdoctoral Fellow, Department of Structural Biology, Stanford University, Stanford, Calif.

Michael L. Quillin, Postdoctoral Fellow, Institute of Molecular Biology, University of Oregon at Eugene

Xiao-Lu Shi, Postdoctoral Fellow, Rockefeller University, New York

Frank G. Whitby, Postdoctoral Fellow, Department of Biochemistry, University of Utah School of Medicine

John Wong, Postdoctoral Fellow, Department of Medicine, Emory University, Atlanta, Ga.

Zhijian Xi, Staff Consultant, Cambridge Technology, Cambridge, Mass.

Chemical Engineering Department (Bioengineering Group)

1986

Gilda Barabino, Associate Professor, Northeastern University, Chemical Engineering Department, Boston, Mass.

Jeffrey Hubbell, Professor of Chemical Engineering, California Institute of Technology, Pasadena

Byung-Geon Rhee, Director, Biotechnology, Sam Yang Co. LTD., Seoul, Korea

1987

Chris Bussineau, Project Leader, Chiron Corporation, Emoryville, Calif.

John Frangos, Professor, University of California, San Diego, Bioengineering Department, La Jolla, Calif.

Todd Giorgio, Associate Professor, Vanderbilt University, Chemical Engineering Department, Nashville, Tenn.

Charles Meyer, Senior Research Engineer, Shell Oil, Environmental Division, Houston.

1988

Robert Cherry, Assistant Professor, Duke University, Mechanical Engineering Department, Durham, N.C.

Pratap Nair, Director, Project Development, Chemshare, Inc., Houston

Timothy Wick, Associate Professor, Georgia Tech University, Chemical Engineering Department, Atlanta, Ga.

1989

Michael Huesemann, Research Engineer, Shell Development, Environmental Division, Houston

Michael B. Lawrence, Assistant Professor, University of Virginia, Biomedical Engineering Department, Charlottesville, Va.

Jonathan F. Petersen, Research Engineer, Failure Analysis Associates, San Francisco, Calif.

Dennis P. Wiesenborn, Assistant Professor, North Dakota State University, Chemical Engineering Department, Fargo

1990

Ralph Cardello, Research Engineer, Exxon, Research and Engineering Control Division, Clinton, N.J.

Susan Casnocha, Research Engineer, Monsanto Research, Life Sciences Division, St. Louis, Mo.

Scott Diamond, Associate Professor, SUNY Buffalo, Chemical Engineering Department, Buffalo, N.Y.

Bernard Folie, Research Engineer, Exxon Polymers, Antwerp, Belgium

Kurt Kunas, Research Engineer, Baxter Healthcare, Chicago, Ill.

Allison Weber, Consultant, Houston

1991

Mark Broussard, Senior Research Engineer, Shell Development, Control Division, Houston

Charlene K. Owens, Research Engineer, Exxon Production Research, Environmental Division, Houston

Sridhar Rajagopalan, Research Engineer, Shell Development, Environmental Division, Houston

Pin Ying Huang, Research Engineer, Exxon Production Research, Environmental Division, Houston

1992

Omid Abbassi, M.D. Resident, Baylor College of Medicine, Houston

Barbara Alevriadou, Assistant Professor, Johns Hopkins University, Biomedical Engineering Department, Baltimore, Md.

Joseph Carosi, Research Engineer, Dow Central Research, Midland, Mich.

Nancy Shu-hui Huang, Research Engineer, Exxon Production Research, Environmental Division, Houston

Hei Chan Lee, Bioprocess Engineer, Tanox Biosystems, Houston

S.C. Niranjan, Research Associate, University of Texas Medical Branch, Galveston

Gerard Tolentino, Research Engineer, Hoechst Celanese, Corpus Christi

1993

Charles Liu, Medical Student, Yale Medical School, New Haven, Conn.

Lance Munn, Instructor, Harvard Medical School, Boston, Mass.

Nicholas Panaro, Postdoctoral Fellow, NIH, Bethesda, Md.

Peng Yu, Research Scientist, Bristol Meyers-Squibb, Syracuse, New York

Chih-Huang Ho, Research Engineer, Biotechnology Institute, Taipei, Taiwan

Jeff McCrary, Assistant Professor, Virginia Polytechnic University, Blacksburg, Va.

John Patton, Staff Scientist, GlycoTech Corporation, Rockville, Md.

1994

Aristos Aristidou, Research Associate, Bioengineering Center, Massachusetts Institute of Technology, Boston

Rajiv Bhadra, Research Associate, Rice University, Houston

David Jones, M.D. Student, Baylor College of Medicine, Houston

Konstantinos Konstantopoulos, Research Associate, Rice University, Houston

Yih Lee, Research Associate, Bioengineering Center, Dartmouth College, Hanover, NH

John Mathew, Research Engineer, Cabot Corporation, Boston, Mass.

Charles Patrick, Research Associate, Rice University, Houston

Julia M. Ross, Assistant Professor Chemical and Biochemical Engineering Department, University of Maryland at Baltimore County, Baltimore

Vinod Palathinkara, Research Associate, Bioengineering Department, University of Oklahoma, Norman

John Wagner, Assistant Professor, Chemical Engineering Department, Tri-State University, Angola, Ind.

Chemistry Department (Biosciences Group)

1986

Leslie Askonas, Research Scientist, Monsanto, St. Louis, Mo.

Robson Mafoti, Research Scientist, Mobay Corporation, Pittsburgh, Pa.

1988

Elizabeth Eudy Gomez, Instructor, Arkansas College, Little Rock

John A. Goodwin, Assistant Professor, Eckerd College Department of Chemistry, St. Petersburg, Fla.

1990

DeAnna K. Coggin, Postdoctoral Research Associate, Purdue University, West Lafayette, Ind.

Shirley A. Moy, Research Scientist, Dow Chemical Company, Houston

1991

Jorge A. Gonzalez, Section Leader, Azko Chemical Company, Hydrocarbon Analysis Division, Pasadena, Tex.

Yan Li, Research Associate, DuPont, Wilmington, Del.

1992

Angelika Muscate, Postdoctoral Fellow, University of California, San Francisco

1995

Ted Arnst, Research Scientist, Nalco Chemical Company, Sugar Land, Tex.

Joseph E. Bradshaw, Postdoctoral Research Associate, University of Pennsylvania School of Medicine, Department of Pharmacology, Philadelphia

Electrical and Computer Engineering Department (Bioengineering Group)

1986

Nirmala Ganapathy, Senior Research Engineer, Exxon Production Research

Darel A. Linebarger, Assistant Professor, University of Texas, Dallas

1989

John A. Halter, Assistant Professor, Baylor College of Medicine, Houston

1990

Anand R. Kumar, Staff Engineer, British Physical Labs, India

1991

Carmen C. Canavier, Research Associate, University of Texas Health Sciences Center, Houston

C. Richard Murphey, Research Associate, University of Texas Medical Branch, Galveston, Tex.

George Pettit, Staff Scientist, Food and Drug Administration, Rockville, Md.

John Shumaker, Research Associate, Houston Advanced Research Center, The Woodlands, Tex.

1992

Jacob Agris, M.D./Ph. D. Resident Physician, Wayne State University, Detroit Med Center

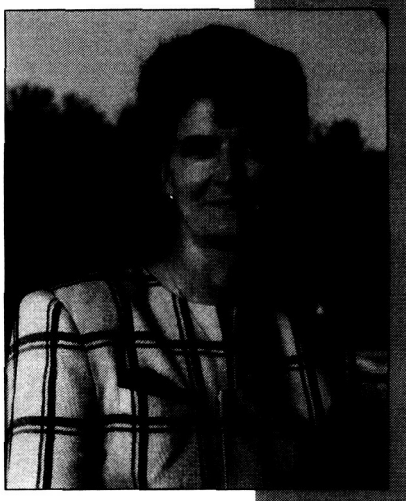
Iyad Saidi, M.D. /Ph. D. Resident Physician, Johns Hopkins, Baltimore, Md.

1995

Miriam Zacksenhouse, Assistant Professor, Technion Israel Institute

John Henry Schild, Postdoctoral Fellow, Baylor College of Medicine, Houston

Outreach and Special Institute Events



Diana L. Welch, Assistant Director of the Institute of Biosciences and Bioengineering

The Institute's outreach efforts are complementary to its primary mission of promoting interaction among faculty and students in the biosciences and bioengineering. Through our outreach efforts, we are instrumental in bringing together individuals from different disciplines and groups that affect and are affected by our research programs, including ethics and public policy, as well as from the biotechnology industry and the general public.

For three days in February-March 1994 the Institute hosted the second DeLange Conference on the Rice University campus entitled "Biotechnology: Science, Engineering and Ethical Challenges for the 21st Century." This conference brought together a diverse audience of scientists, engineers, politicians, ethicists, and concerned laypersons to discuss both the great opportunities and the difficult challenges that progress in biotechnology presents. A book based on this conference is being published by the Joseph Henry Press, an arm of the National Academy of Sciences Press, and is scheduled for completion this December. The purpose of the conference and of this resulting publication is to contribute to and encourage broad participation in the important dialogue that will shape the direction of biotechnology in the twenty-first century.

This year our special outreach efforts included the third offering of the Annual Advances in Tissue Engineering course and a one-day workshop presented by the Southwestern Regional Office of the FDA Biologics Division designed to bring together representatives of the biotechnology industry to assist them in efficient and successful attainment of product marketing approvals for products from the FDA.

This year we also received an award for $5 million over five years from the National Aeronautics and Space Administration (NASA) to establish the Institute as a NASA center of research and training in gravitational biology.

Details of these events are highlighted on the following pages.

Establishment of the Institute as a NASA Specialized Center of Research and Training in Gravitational Biology

We are pleased to reprint here an article from the September 21, 1995, *Rice News:*

NASA Grants Rice $5 Million for Center: Institute of Biosciences and Bioengineering to Study Microgravity

BY LIA UNRAU
Rice News Staff

The Institute of Biosciences and Bioengineering at Rice has been awarded a $5 million, five-year grant to serve as a NASA Specialized Center of Research and Training (NSCORT).

NASA's Johnson Space Center (JSC) is a collaborating partner in the Rice NSCORT project. The specialized center will seek to understand the effects of Earth's gravity on living cells.

The National Aeronautics and Space Administration (NASA) established the NSCORT program to create effective methods for solving specific problems in space life sciences. North Carolina State University, in collaboration with Wake Forest University, and Rutgers University, in collaboration with Stevens Institute of Technology, are also new NSCORTs, bringing the total number of specialized centers in the United States to eight.

As a designated gravitational biology center, researchers from Rice and the JSC will study how gravity, or the lack of it, affects cell functions and assemblies of cell tissues. In its report, the NSCORT review team concluded that "this multifaceted, basic research-oriented proposed NSCORT will establish the effects of micro-and hypergravity on a number of interesting biological systems." The report also stated that, "Given the quality control of this NSCORT and the expertise of the scientists, the results should be fundamental to gravitational biology; thus, this will provide an excellent contribution to NASA's mission."

Rice and JSC scientists will look at the effects of microgravity and associated environmental stresses on cellular metabolic response.

"We've shown, and others have too, that gravitational forces affect what cells do, what they are, and what they make," said Larry V. McIntire, chair of the Institute of Biosciences and Bioengineering and the new specialized center's director. "A lot of work has previously been done on animal models," McIntire said, "What we proposed is to look at molecular mechanisms, and we hope to understand how environmental stresses, such as altered gravity, affect cell functions at the molecular level.

"The hope is that if we understand the functions on a molecular level, we can develop measures that would counter these problems on other levels."

The proposal included a series of projects with faculty members investigating the effects of the gravitational environment on various model cell systems. At this time, all research is ground-based, but researchers hope some projects will develop into space flight experiments.

The Institute of Biosciences and Bioengineering has had an ongoing relationship with JSC since the early '80s, when the two centers collaborated on creating bioreactors, which simulate some aspects of microgravity, or weightlessness.

"This project will greatly enhance the interaction of a much broader group of faculty," McIntire said. Researchers at JSC will participate in a seminar series and teach some courses.

As part of the NSCORT program, the center will hold an open symposium focusing on advances in gravitational biology each year. At the end of the five-year program, an International Space Biology Symposium will be held jointly with the Johnson Space Center.

Included in the proposal is the introduction of a new course at Rice in gravitational biology.

The center will receive $1 million each year for the next five years. The money will provide support for undergraduates, graduate students, and postdoctoral researchers as well as equipment and supplies for research.

"It's becoming clearer and clearer that learning about the coupling of local mechanical environments and cell function has a huge spin-off in other areas," McIntire said. "It's important to understanding pathologies here on Earth involving the cardiovascular system, bone, and muscle."

A major medical problem associated with space flight is bone resorption (where the bone cells remove material they had previously deposited) and demineralization. Studying bone formation with respect to gravity and microgravity promises insights into developing cures and prevention methods for the effects of not only space flight but also long-term bed rest and possibly natural diseases such as osteoporosis, McIntire said. Research into how weight, pressure, and the lack of it affects flow against endothelial cells, the cells that line blood vessels, can also be applied to diseases such as arteriosclerosis.

In studying mammalian cells, scientists will examine the long-term effects of weightlessness on loss of bone and muscle, decreased immune response, and blood flow.

The inherent nature of the institute played a role in securing the grant for Rice, McIntire said. "I think what made us competitive for the grant is that our structure crosses departmental lines, and we have input from both the biosciences and bioengineering," he said. Rice faculty were

already conducting research in closely related areas as well.

"There is a good mix of investigators in this project," McIntire said, "from developmental biology, microbiology, cell biology, and a wonderful mix of young to more senior investigators."

The series of projects involves nine Rice faculty members and four researchers from JSC. Three investigators will study effects of gravity on immune cells: McIntire; Neal Pellis, program director of biotechnology with NASA/JSC; and Kyriacos Zygourakis, professor of chemical engineering.

Kathleen Beckingham, professor of biochemistry and cell biology, and Michael Stern, assistant professor of biochemistry and cell biology, will examine simulated microgravity forces on cellular development in fruit flies.

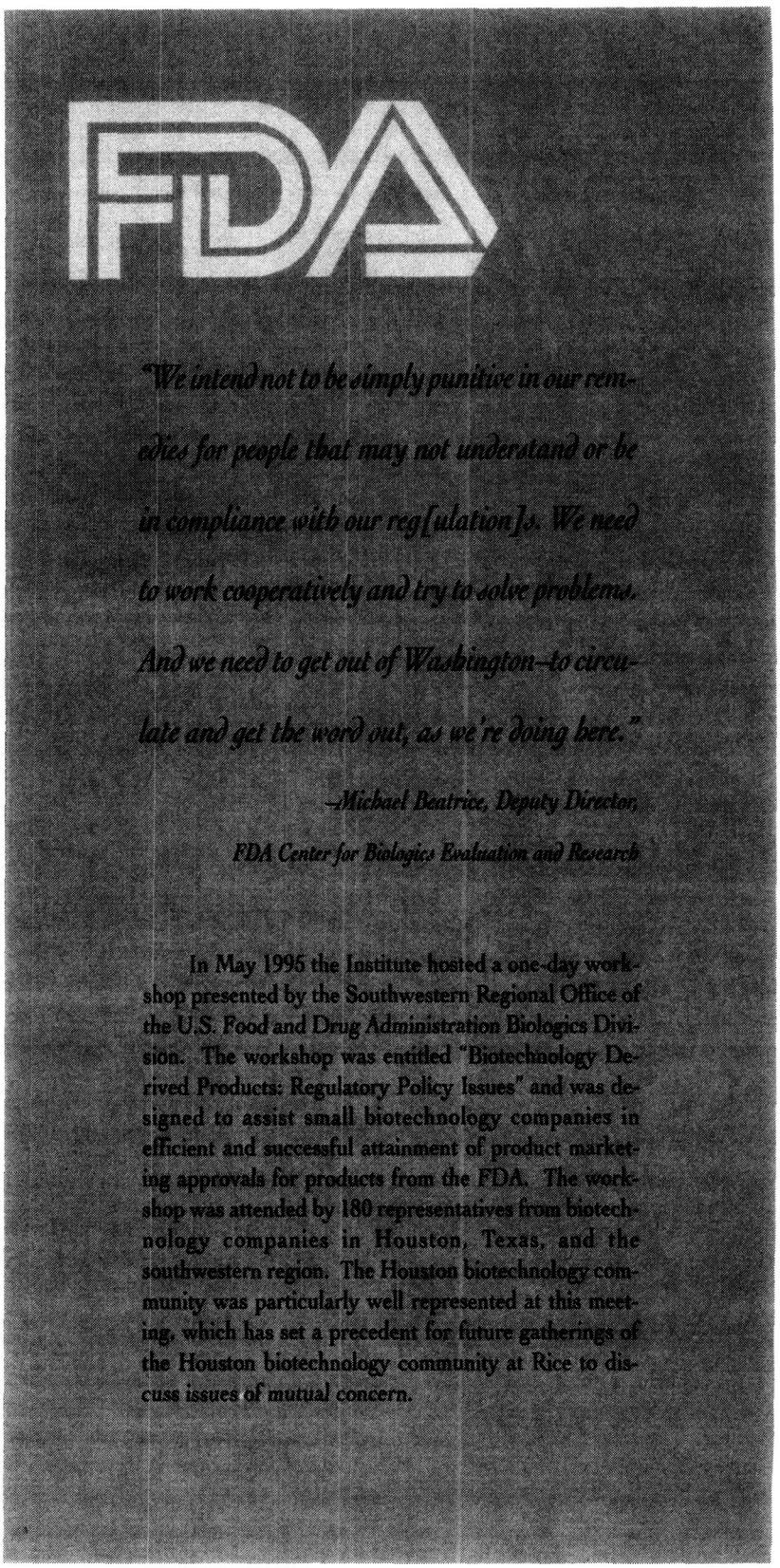
Michael Gustin, associate professor of biochemistry and cell biology, will study pressure and sensing genes in yeast cells, and Janet Braam, assistant professor of biochemistry and cell biology, will research molecular and developmental responses in plants.

Antonios G. Mikos, assistant professor of chemical engineering, is studying bone formation and Daniel Feeback, research scientist at NASA/JSC, is looking at the effects on muscle and fiber formation.

George Bennett, professor of biochemistry and cell biology, and Fred Rudolph, professor and department chair of biochemistry and cell biology, are examining the effects of microgravity on bacteria-host interactions.

Two researchers from Johnson Space Center, Clarence Sams and Peggy Whitson, are studying the effects of microgravity on the cytoskeleton and interactions of the immune system.

FDA Workshop: "Biotechnology Derived Products: Regulatory Policy Issues"



3rd Annual "Advances in Tissue Engineering" Short Course

The next generation of therapeutics for a number of acquired or inherited diseases will be patient-specific, utilizing cells, tissues, and eventually bioartificial organs for transplantation. To bring professionals up-to-date in this field, the Institute of Biosciences and Bioengineering, in conjunction with the Rice University School of Continuing Studies, sponsored the third annual intensive week-long continuing education course entitled "Advances in Tissue Engineering" August 1-5, 1995.

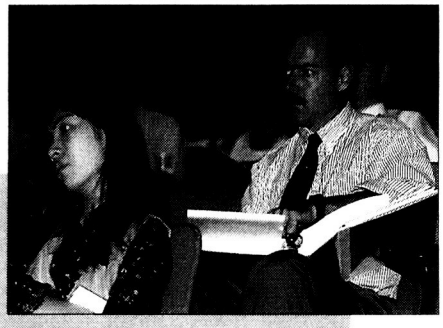
The course surveyed the latest knowledge and technologies in the world of patient-specific therapeutics, from transplantation of cells and tissues to bioartificial organs. Cell-based therapies and artificial organs can have a great impact in medicine for treatment of inherited diseases, such as liver disease, diabetes, Parkinson's, and other organ deficiencies.

Twenty faculty from Rice, the Texas Medical Center, industry, and other institutions working on advances in the science and technology of tissue engineering presented the course, which was organized and directed by Dr. Antonios G. Mikos, T. N. Law Assistant Professor of Chemical Engineering and Bioengineering in the Institute of Biosciences and Bioengineering. Instructors included Institute faculty and guest faculty from many fields, including biochemistry, biomedical engineering, and orthopaedic surgery.

The course reviewed the recent advances in biochemistry and biophysics; cell, molecular, and developmental biology; and modern materials science. It focused particularly on the science and technology of tissue engineering and the development of new means of replacing damaged or diseased body parts and restoring function. It also assessed the prospects and directions for development of strategies to regenerate metabolic organs and repair connective tissues and cell therapies to deliver proteins and other therapeutic drugs.

The purpose of the course is to provide scientists and clinicians with a way to quickly update their knowledge in this rapidly growing, interdisciplinary field.

This year twenty-six people from twelve states and six foreign countries attended. The course has generated new collaborations among Institute investigators and their counterparts at Baylor College of Medicine and the M.D. Anderson Cancer Center and this year received an endorsement from the American Society of Biomaterials.

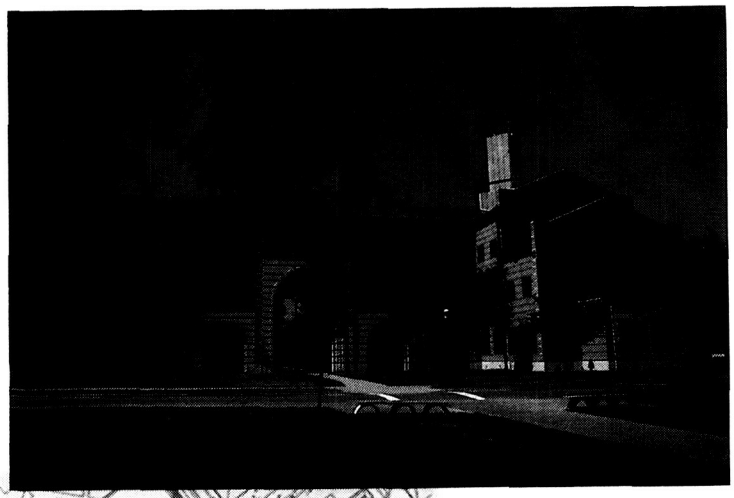


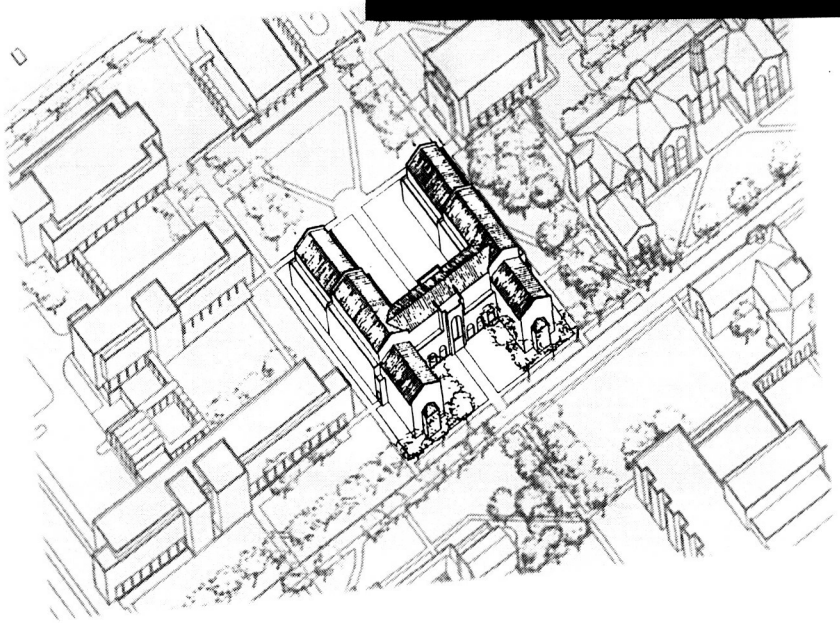
Dr. Antonios G. Mikos, course director for "Advances in Tissue Engineering," discusses a point with course attendee Dr. Vera Donati from the University of Milan Institute of Plastic Surgery (left). Dr. Gail Naughton, executive vice president and chief operating officer for Advanced Tissue Engineering, Inc. in La Jolla, Calif., presents a lecture on new technologies for cell and tissue culture (top, center).

For more information about the course or to be put on the mailing list to receive information about the next course, contact the Rice University School of Continuing Studies, (713) 520-6022 or 527-4805.

Brief History of the Institute

The Institute of Biosciences and Bioengineering was established in 1986 in recognition of the revolutionary advances in biotechnology and with the purpose of building on existing strengths in biochemical and biomedical engineering and biosciences at Rice. The goal of the Institute is to provide an organizational framework for fostering interaction among the biological, chemical, and engineering disciplines, both between research groups at Rice and between life scientists, bioengineers, and medical colleagues at other institutions. In addition, the Institute has a mission to strengthen the cross-disciplinary educational programs at the undergraduate, graduate, and postgraduate levels.





Members of the Institute include thirty faculty from the Departments of Biochemistry and Cell Biology, Chemistry, Chemical Engineering, and Electrical and Computer Engineering and seventeen faculty members from the Texas Medical Center, providing a broad mix of interests and expertise. The biochemical and biomedical faculty in chemical engineering is the second largest in the country. Research is carried out in three major laboratories that make up the Institute: The Cox Laboratory for Biomedical Engineering, the Mabee Laboratory for Biochemical and Genetic Engineering, and the Greenwood Laboratory for Basic Medical Science. Faculty can be members of more than one laboratory.

Since its inception, the Institute has made major advances toward its goals. Following are highlights of some of these accomplishments.

"Combining the new fields of molecular biology and biomedical engineering in George R. Brown Hall has created a unique research and teaching facility at Rice, with the purpose of promoting cross-disciplinary interactions in biotechnology."

Larry McIntire, at the dedication ceremony of George R. Brown Hall, November 1991

Completion of George R. Brown Hall

In 1989 efforts were begun to create a world class state-of-the-art biotechnology facility to house the Institute of Biosciences and Bioengineering. This new $25-million, 108,000 square-foot facility, the George R. Brown Hall, was completed in 1991. The Institute moved into George R. Brown Hall in August of that year.

The establishment of George R. Brown Hall as the home for the Institute of Biosciences and Bioengineering was a pivotal point in the development of the Institute. It established a physical identity and symbolized a standard of excellence for the Institute, and it provided a means of greatly increasing the potential for interdisciplinary interaction by physically bringing together life scientists and bioengineers into one facility.

Quite symbolically, the location of the building between the biological sciences building on the west and the chemistry and engineering buildings on the east reinforces the Institute's mission to bridge these disciplines.

Building Dedication and Symposium

On November 1, 1991, George R. Brown Hall was formally dedicated. In conjunction with the dedication of the building, the Institute presented its first symposium entitled "Perspectives in Biotechnology: Cross-Disciplinary Research and Training in Biosciences and Bioengineering." The principal speakers at the symposium were Dr. Purnell W. Choppin (president, Howard Hughes Medical Institute), Dr. Daniel I. C. Wang (director, Bioprocess Engineering Research Center, Massachusetts Institute of Technology), and Dr. David Botstein (chair, Department of Genetics, Stanford University). These inaugural events were well attended and provided a means of formally introducing the Institute to the Rice community and the greater Houston scientific and business communities.

R&D Laboratory of the Year Award to George R. Brown Hall

George R. Brown Hall received the 1992 "Laboratory of the Year" Award from *Research and Development* magazine and was featured in the May 1992 issue as well as in the April 1992 issue of *Architecture* magazine. The June 25, 1992, issue of *Nature* magazine featured a fifteen-page section titled "Science in Texas," in which the Institute and George R. Brown Hall were featured.

NIH Biotechnology Training Grant

In 1990 the Institute was awarded a five-year grant from the National Institutes of Health, National Institute of General Medical Sciences, for a Biotechnology Training Program. The program provides support in a variety of disciplines for graduate students interested in a research career in biotechnology. This year the Institute was awarded a five-year renewal of this training grant, providing support for graduate students through 1999.

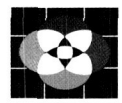
First Institute Publications

To increase the visibility of the Institute to the outside world, to improve communication with Institute donors and the greater Rice community, and to help recruit graduate students, the first graduate recruitment poster and Institute brochure were produced and distributed in the fall of 1991 and spring of 1992, respectively. A revised Institute brochure and our first Annual Report were published in 1994.

Faculty Recruitment

The existence of the Institute and the new facilities in George R. Brown Hall were instrumental in the successful recruitment of several new faculty members. During the first five years of the Institute, six new faculty were recruited to the Institute member departments. Drs. Michael Gustin, Richard Gomer, Janet Braam, and Michael Stern joined the Department of Biochemistry and Cell Biology, and Drs. Jacqueline Shanks and Antonios Mikos joined the Department of Chemical Engineering. The Institute continues to attract bright new faculty members, with the addition in 1993 of Drs. Susan Gibson and Edward Nikonowicz, and most recently, Drs. Bonnie Bartel, Eugenio de Hostos, and Seiichi Matsuda.

Institute Directory



Institute Directors

Larry V. McIntire, Ph.D.
Chair of the Institute of Biosciences and Bioengineering and Director of the Cox Laboratory for Biomedical Engineering

Frederick B. Rudolph, Ph.D.
Executive Director of the Institute of Biosciences and Bioengineering and Director of the Mabee Laboratory for Biochemical and Genetic Engineering

George J. Schroepfer, Jr., M.D. , Ph.D.
Director of the Greenwood Laboratory for Basic Medical Science

Institute Faculty

Rice University

Bonnie Bartel, Assistant Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Kathleen M. Beckingham, Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

George N. Bennett, Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Janet Braam, Assistant Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

J. Wayne Campbell, Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

James Clarage, Member of the Mabee Laboratory

John W. Clark, Jr., Professor of Electrical and Computer Engineering, Member of the Cox Laboratory

Eugenio L. de Hostos, Assistant Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Susan I. Gibson, Assistant Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Raymon M. Glantz, Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Richard H. Gomer, Associate Professor of Biochemistry and Cell Biology, Howard Hughes Medical Institute Assistant Investigator, Member of the Mabee Laboratory

Michael C. Gustin, Associate Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

J. David Hellums, Hartsook Professor of Chemical Engineering, Member of the Cox Laboratory

Seiichi P. T. Matsuda, Assistant Professor of Chemistry and Biochemistry and Cell Biology, Member of the Mabee Laboratory

Kathleen S. Matthews, Wiess Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Antonios G. Mikos, Law Assistant Professor of Chemical Engineering and Bioengineering, Member of the Cox Laboratory

Joel L. Moake, Professor of Medicine (Baylor), and Associate Director of the Cox Laboratory

Edward P. Nikonowicz, Assistant Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

John S. Olson, Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Graham A. Palmer, Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Ronald J. Parry, Professor of Chemistry, Member of the Mabee Laboratory

George N. Phillips, Jr., Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Maureen G. Price, Member of the Mabee Laboratory

Ka-Yiu San, Associate Professor of Chemical Engineering, Member of the Cox Laboratory and the Mabee Laboratory

Jacqueline V. Shanks, Associate Professor of Chemical Engineering, Member of the Cox Laboratory and the Mabee Laboratory

Michael Stern, Assistant Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Charles R. Stewart, Professor of Biochemistry and Cell Biology, Member of the Mabee Laboratory

James B. Walker, Professor Emeritus of Biochemistry and Cell Biology, Member of the Mabee Laboratory

Lon J. Wilson, Professor of Chemistry, Member of the Mabee Laboratory

Kyriacos Zygourakis, Professor of Chemical Engineering, Member of the Cox Laboratory

Texas Medical Center Adjunct Faculty

Clarence P. Alfrey, M.D., Ph.D. (Baylor), Adjunct Professor, the Cox Laboratory

Suzanne G. Eskin, Ph.D. (Texas Biotechnology Corp-Houston), Adjunct Professor, the Cox Laboratory

Guillermo Gutierrez, M.D. (UT Hlth Sci Ctr Houston), Adjunct Associate Professor, the Cox Laboratory

Michael H. Kroll, M.D. (Baylor), Adjunct Assistant Professor, the Cox Laboratory

Edward C. Lynch, M.D. (Baylor), Adjunct Professor, the Cox Laboratory

Michael Miller, M.D. (UT M.D. Anderson Cancer Center), Adjunct Assistant Professor, the Cox Laboratory

Martin D. Phillips, M.D. (UTHSC), Adjunct Associate Professor, the Cox Laboratory

Jan F. M. Post, M.D, (UTMB,Galveston), Adjunct Assistant Professor, the Cox Laboratory

Joseph Rodarte, M.D. (Baylor), Adjunct Professor, the Cox Laboratory

Andrew I. Schafer, M.D. (Baylor), Adjunct Professor, the Cox Laboratory

David A. Sears, M.D. (Baylor), Adjunct Professor, the Cox Laboratory

Scott I.Simon, Ph.D., (Baylor), Adjunct Assistant Professor, the Cox Laboratory

C. Wayne Smith, M.D. (Texas Children's Hospital-Houston), Adjunct Professor, the Cox Laboratory

Mark M. Udden, M.D. (Baylor), Adjunct Associate Professor, the Cox Laboratory

Kenneth K. Wu, M.D. (UT Hlth Sci Ctr Houston), Adjunct Professor, the Cox Laboratory

Michael Yaszemski, (Wilford Hall Med Ctr) Adjunct Assistant Professor, the Cox Laboratory

Frank M. Yatsu, M.D. (UT Hlth Sci Ctr Houston), Adjunct Professor, the Cox Laboratory

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Diana L. Welch, Assistant Director of the Institute of Biosciences and Bioengineering

Patricia A. Gibbons, Program Coordinator

Rice University seeks to attract to its faculty, staff, and student body qualified persons of diverse backgrounds. In accordance with this policy, Rice does not discriminate in admissions, educational programs, or employment against any individual on the basis of sex, sexual preference, race, color, religion, age, national or ethnic origin, or handicap. University policy also includes affirmative action in seeking to attract to Rice women, minority group members, handicapped individuals, and veterans.